Archives of Internal Medicine

VOLUME 57 APRIL 1936 NUMBER 4

COPYRIGHT, 1936, BY AMERICAN MEDICAL ASSOCIATION

A STUDY OF THE LOWER LOBE OF THE LUNG

AN EXPLANATION OF ROENTGENOLOGIC SHADOWS

JOSEPH LEVITIN, M.D.

AND

HAROLD BRUNN, M.D.

SAN FRANCISCO

The interpretation of roentgenograms is dependent on two essential factors: (1) knowledge of the anatomy of the part examined, and (2) an interpretation of the disease process in terms of variations in density noted on the roentgenogram. Any addition to the knowledge of roentgenologic anatomy would aid in the interpretation and localization of shadows seen on the roentgenogram. This paper is presented as a contribution to the roentgenologic knowledge of the anatomic structure of the lower lobes of the lungs.

Anatomically, the right lung is divided into three lobes, the upper, the middle and the lower, by two interlobar fissures, and the left lung is divided into two lobes, the upper and the lower, by one interlobar fissure. The course of the major fissures on both sides is from the level of the spinous process of the third dorsal vertebra posteriorly, obliquely downward and forward to the costochondral articulation of the sixth rib anteriorly. On the right side another fissure extends horizontally forward from the axilla to the costochondral articulation of the fourth rib. It separates the superior lobe above and the inferior lobe below.

Our studies indicate that the lower lobe on each side is divided into two parts. The division can be proved anatomically, embryologically and by a study of the bronchial distribution to the lower lobe. At times, a fourth lobe on the right side and a third lobe on the left side may be present as an anomaly when fusion between the two divisions of the lower lobe has failed to take place. Each of the two divisions may be, and often is, separately involved by a disease process, and each gives different shadows on the roentgenogram. We have called the upper part of the lower lobe the superior division and the lower portion the inferior division. In the lateral view the superior division is well

This work was assisted by a grant from the Lily Spreckels Weggeforth Fund.

From the Department of Roentgenology, Mount Zion Hospital, and the University of California Thoracic Clinic.

seen on the roentgenogram as a triangular area posteriorly placed, with the apex at the hilus. The upper border of this division corresponds to the interlobar septum between the upper and the lower lobe. The lower border corresponds to an imaginary line drawn from the hilus backward and downward to the eighth rib posteriorly. The second, or inferior, division of the lower lobe is the major division and takes up the remaining portion of the area occupied by the lobe (fig. 1).

A study of the bronchi distributed to the lower lobe again marks out the division of the superior and inferior portion of the lower lobe. Two distinct bronchial distributions are always present to the two divisions of the lobe. This fact was established by a study of roentgenograms of postmortem specimens, with the bronchi of the lower lobe filled with 30 per cent bismuth subnitrate in petrolatum.

The first branch from the main bronchus to the lower lobe of the right lung rises opposite the bronchus of the middle lobe. This branch

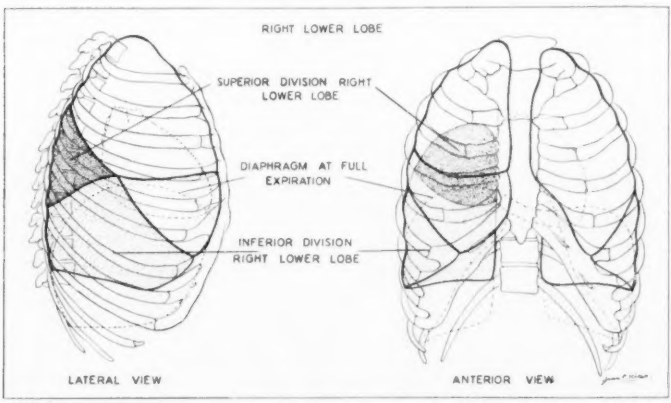


Fig. 1.—Diagram of the lower lobe of the right lung. The lower lobe of the left lung has a similar superior and inferior division; for the sake of brevity and clarity it has been omitted.

is directed posteriorly and soon divides into smaller branches, all of which are distributed only in the superior division. In the left lung the first branch rises from the main bronchus at the same level, in a comparable position, and is likewise directed posteriorly. The main stem of the bronchus to the lower lobe continues downward for about 1 cm. and then divides into three secondary bronchi in the right lung and two secondary bronchi in the left lung. These bronchi are distributed only to the inferior division (fig. 2). There is no overlapping of bronchial distribution between the superior and the inferior division. They are as distinct from one another as the bronchi to the upper lobe are distinct from the bronchi to the middle lobe.

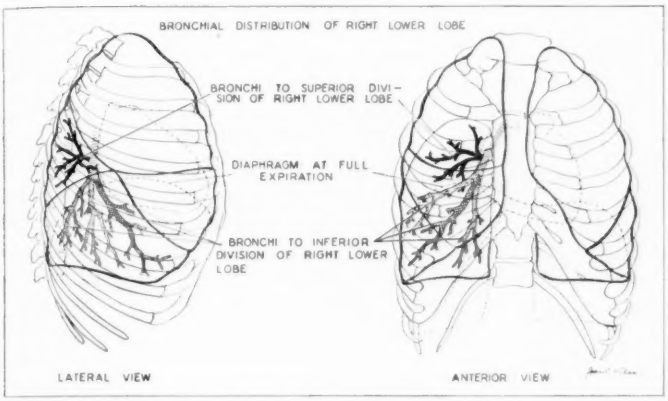

BRONCHIAL DISTRIBUTION OF RIGHT LOWER LOBE
BRONCHI TO SUPERIOR DIVISION OF RIGHT LOWER LOBE
DIAPHRAGM AT FULL EXPIRATION
BRONCHI TO INFERIOR DIVISION OF RIGHT LOWER LOBE
LATERAL VIEW
ANTERIOR VIEW

Fig. 2.—Diagram of the bronchial distribution of the lower lobe of the right lung. The lower lobe of the left lung has a similar division of the bronchi; for the sake of brevity it has been omitted.

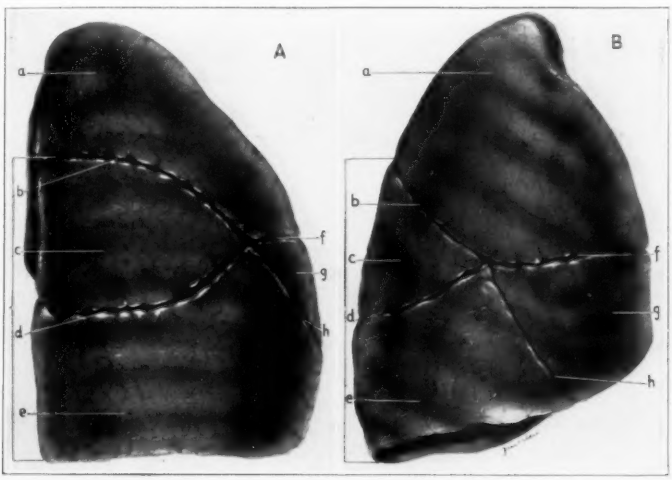


Fig. 3.—*A* is a diagrammatic drawing of the posterior view of a four-lobed right lung. *B* is a diagrammatic drawing of the lateral view. In both drawings *a* indicates the upper lobe; *b*, the fissure between the upper and the lower lobe; *c*, the superior division of the lower lobe; *d*, the fissure dividing the lower lobe into two parts; *e*, the inferior division of the lower lobe; *f*, the fissure between the upper and the middle lobe; *g*, the middle lobe, and *h*, the fissure between the middle and the lower lobe. The bracket indicates the lower lobe.

An intralobar fissure may be observed completely dividing the two parts, similar to the interlobar fissure dividing the main lobes, as described previously. The division of the lower lobe by a fissure may be partial or complete. Figure 3 depicts a right lung removed at autopsy, showing the lower lobe divided into a superior and an inferior division by a complete fissure. Fusion had failed to take place. It is not uncommon to note a shallow fissure or a sharp dimpling in a normal specimen, marking the limit of fusion of the superior to the inferior part of the lower lobe (fig. 3 *A* and *B*).

It is interesting to know that this division of the lobe has an embryonic origin which determines its distinct bronchial distribution. In a review of the embryonic development of the bronchi (Keibel and

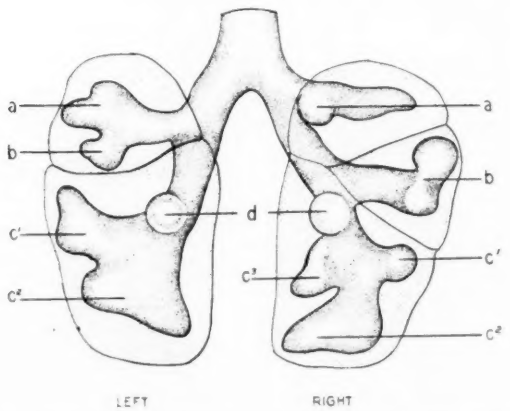


Fig. 4.—An embryo at the beginning of the fifth week, viewed from behind. In this illustration *a* indicates the bronchus to the upper lobe; *b*, the bronchus to the middle lobe on the right side and to the upper lobe on the left side; c^1 and c^2, bronchi to the inferior division of the lower lobe; c^3, the infracardial bronchus on the right side to the lower lobe, and *d*, the bronchus to the superior division of the lower lobe. (From Keibel and Mall,[1] after Merkel, 1902.)

Mall[1]) one notes that the bronchus to the superior division of the lower lobe develops from an anlage which is distinct from the anlage of the bronchi to the inferior division of the lower lobe. In an embryo of 11 mm. the anlage for the main bronchi is well established (fig. 4). On the right side is the anlage of the apical bronchus (*a*), extending dorsolaterally, which is to supply the upper lobe of the right lung. The anlage for the lateral first ventral bronchus (*b*) is present to supply

1. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 482.

the middle lobe. The left side differs in that the anlage *a* and *b* have a common stem to supply the single upper lobe. Next in order is the anlage *d*, which arises separately and develops into the bronchus for the superior division of the lower lobe. The main stem continues downward and ventrally and gives rise to two main bronchial anlagen on the left (c^1 and c^2) and three on the right. The additional bronchial anlage on the right side is for the infracardial bronchus (c^3).

A 13 mm. embryo shows the anlage for the lobes well established and explains the formation of the fissures (fig. 5). On the right side are a bud for the upper lobe (*A*) *and one for the middle lobe* (*B*). There is a small, shallow furrow between them which will form the interlobar fissure. On the left side one large bud contains the bronchi

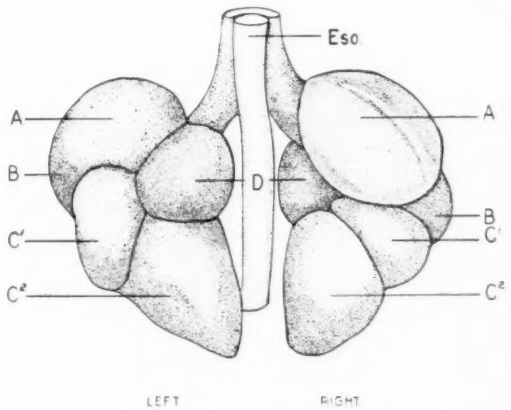


Fig. 5.—Lung anlage of an embryo of about 13 mm., viewed from behind. *A* indicates the lung bud for the upper lobe; *B*, the lung bud for the middle lobe on the right side (note how on the left side the comparable bud is joined with *A* to form a large upper lobe); C^1 and C^2, lung buds for the inferior division of the lower lobe, and *D*, the lung bud for the superior division of the lower lobe. (From Keibel and Mall,[1] after Blisnianskaja, 1904.)

(*A* and *B*) for the single upper lobe of the left lung. Three buds are present for the lower lobe (C^1, C^2 and *D*). Of particular note is the bud for the dorsal bronchus (*D*). This is definitely separated by a furrow from the other buds. If the furrow persists, a fissure will be present separating this part of the lobe, resulting in four distinct lobes on the right and three distinct lobes on the left side (fig. 3). If a complete fusion of all the lung buds of the lower lobe takes place, the result will be a single lower lobe. This follows the anatomic description as previously given and as described in textbooks of

anatomy. If fusion of the buds is incomplete, a fissure will remain, with a reflection of pleura, producing an intralobar fissure. On the roentgenogram the fissure can sometimes be seen as a pleural line extending from the parietal pleura into the parenchyma of the lung. This shadow has often been misinterpreted as a pleural adhesion. The fissure may extend all the way to the hilus, completely dividing the lower lobe into two distinct lobes (fig. 3).

Other writers have recognized two divisions of the lower lobe, either anatomically or as affected by a disease process, without recognizing the anatomic basis or the embryologic origin for this division.

Pohl [2] described the apical region of the lower lobe as sometimes set off so as to become an independent lobe. He stated that it is noted frequently at autopsy and is recognizable roentgenologically only in a pathologic state.

Kramer and Glass [3] studied the roentgenologic localization of abscess of the lung and divided the lung into segments corresponding to the main bronchial divisions. They set off an apical posterior triangular area, which they called the apical middle paravertebral segment. This is similar to the superior division already described.

The superior division of the lower lobe is the one most frequently involved in pneumonic processes. At present we can offer no explanation for this. The bronchi to this part of the lobe are the only ones that are directed posteriorly, so that with the patient in the prone position they are the most dependent bronchi. The action of gravity on secretions in these bronchi may be of some significance. The appearance on the roentgenogram of a disease process in this part of the lobe depends on the position of the diaphragm. If the chest is well expanded and the diaphragm is low, the disease process appears relatively high in the chest. Shadows of this sort often have been interpreted roentgenologically as evidence of central pneumonia. The physical signs of the process are all posterior, in a small area between the vertebral border of the scapula and the vertebral column and from the fourth to the eighth rib.

OBSERVATIONS ON CASES

The roentgenograms for case 1 are illustrative of the appearance of a pneumonic process in the superior part of the lobe when the diaphragm is at full inspiration.

CASE 1 (fig. 6).—In J. W., a man aged 63, on the third day following an operation for a ventral hernia cough developed, and the temperature rose to

2. Pohl, R.: Der Lobus Posterior der Lunge, Fortschr. a. d. Geb. d. Röntgenstrahlen **46**:583 (Nov.) 1932.

3. Kramer, B., and Glass, A.: Bronchoscopic Localization of Lung Abscess, Ann. Otol., Rhin. & Laryng. **41**:1210, 1932.

38 C. (100.4 F.). Physical signs were not present at first, but the next day an area of dulness with impaired breath sounds was noted on the right side posteriorly. A roentgenogram showed an area of increased density extending from the hilus in the middle of the pulmonary field. The condition was diagnosed central pneumonia. The lateral view showed the process to lie posteriorly, to be triangular and to conform closely to the area designated as the supe-

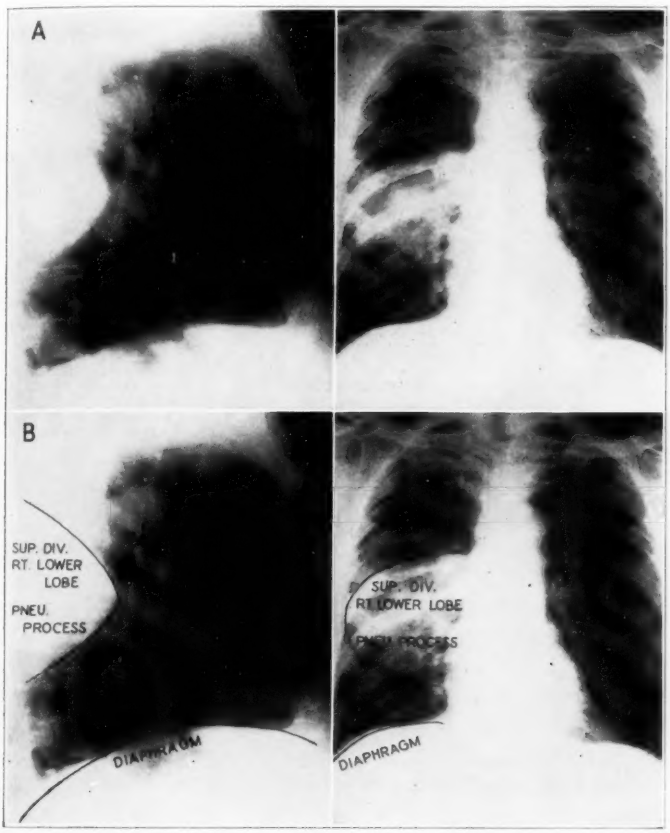


Fig. 6.—A pneumonic process involving the superior division of the lower lobe of the right lung. The diaphragm is at full inspiration. This is often called central pneumonia.

rior division of the lower lobe. The process in the lobe developed into an abscess of the lung, and the patient subsequently died. Autopsy confirmed anatomically the location of the process.

The roentgenograms for case 2 illustrate the appearance of the process when the diaphragm is in midway position.

Case 2 (fig. 7).—J. C., a man aged 37, had a history of an inflammatory process, following an operation, which developed into a chronic abscess of the lung. The diaphragm on the right side was considerably higher than that on the left, and in the postero-anterior view the area of involvement appeared to occupy the lower half of the chest. The lateral view clearly demonstrated the posterior location of the process, which was triangular and conformed closely to the outline of the superior division of the lower lobe.

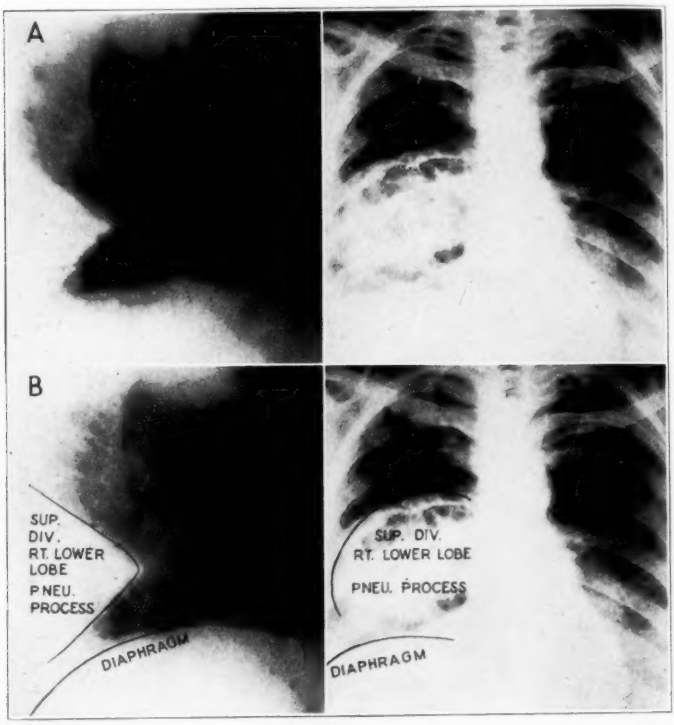


Fig. 7.—A pneumonic process involving the superior division of the lower lobe of the right lung. The diaphragm is in a midway position.

The roentgenograms for case 3 also illustrate the appearance of a pneumonic process in the superior division of the lower lobe when the diaphragm is partially elevated.

Case 3 (fig. 8; courtesy of Dr. E. Wolff).—E. M., a boy aged 7 years, had a sudden onset of fever, with pain in the right side of the chest and rapid respiration. Physical examination showed an area of dulness in the right side of the chest posteriorly, with diminished breath sounds. The diagnosis was pneumonia of the lower lobe of the right lung. The roentgenogram of the postero-anterior

view showed an area of increased density occupying the lower half of the right side of the chest. The lateral view showed the process to lie posteriorly in the region of the superior division of the lower lobe.

When the diaphragm is at the full extent of expiration the highest point lies on a level with the fourth rib anteriorly. If the superior division of the lower lobe is involved by a pneumonic process this part

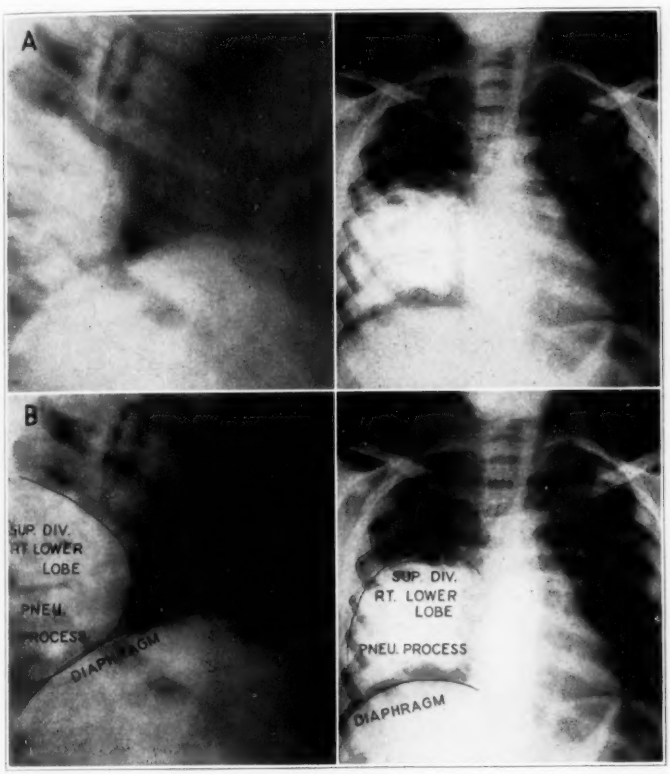


Fig. 8.—A pneumonic process in the superior division of the lower lobe of the right lung. The diaphragm is partially elevated.

of the involved lung appears to lie in the recess behind the diaphragm. It may be mistaken for encapsulated fluid.

The roentgenograms for case 4 illustrate a pneumonic process in the superior part of the lobe and its appearance with the diaphragm at full expiration.

Case 4 (fig. 9; courtesy of Dr. A. L. Brown).—H. D., a girl aged 4½ years, had a sudden onset of abdominal pain in the right lower quadrant, which gradually spread through the whole abdomen. The temperature was 102 F. A diagnosis of acute appendicitis was made. At operation pneumococcic peritonitis was noted. The temperature postoperatively continued to be about 40 C. (104 F.), the pulse rate was from 130 to 140, and the respiratory rate was from 30 to 40. Three weeks following the operation a roentgenogram of the chest showed grayness at the base of the right lung, well seen in the lateral view as a dense, well

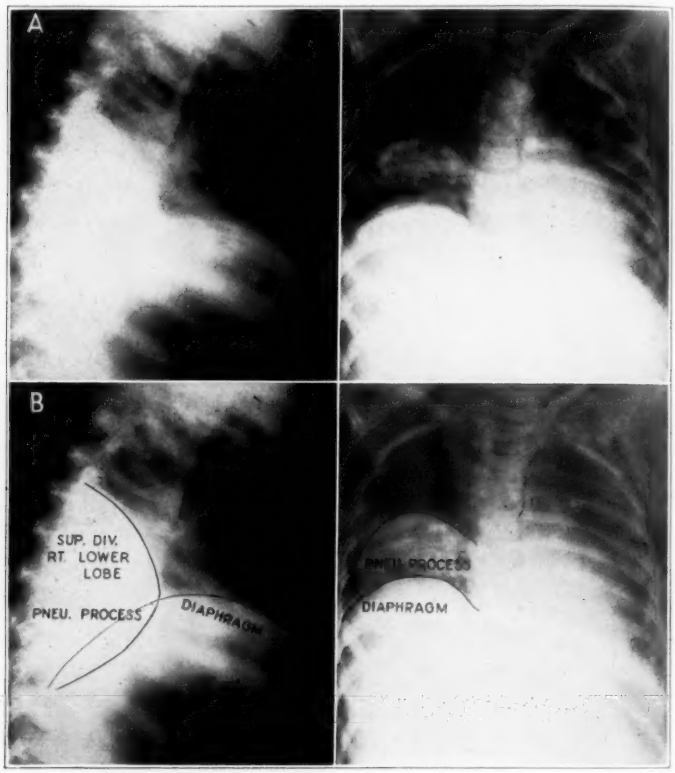


Fig. 9.—A pneumonic process in the superior division of the lower lobe of the right lung. The diaphragm is elevated. The disease process appears to lie in the recess behind the diaphragm. It was misinterpreted as encapsulated fluid.

demarcated shadow lying in the posterior recess behind the diaphragm. Interpretation of the roentgenogram was: encapsulated fluid. Repeated attempts at aspiration failed to obtain fluid. Further study of the shadow, its location and shape, showed its close similarity to the area occupied by the superior division of the lower lobe. The diagnosis was then changed to that of pneumonic consolidation of this part of the lobe. The further clinical course confirmed the diagnosis.

The inferior division of the lower lobe, while not as frequently involved by disease processes, also has its characteristic shadow. Most of the involved area of the lung is masked by the shadow of the liver. In the postero-anterior view, an area of increased density is shown

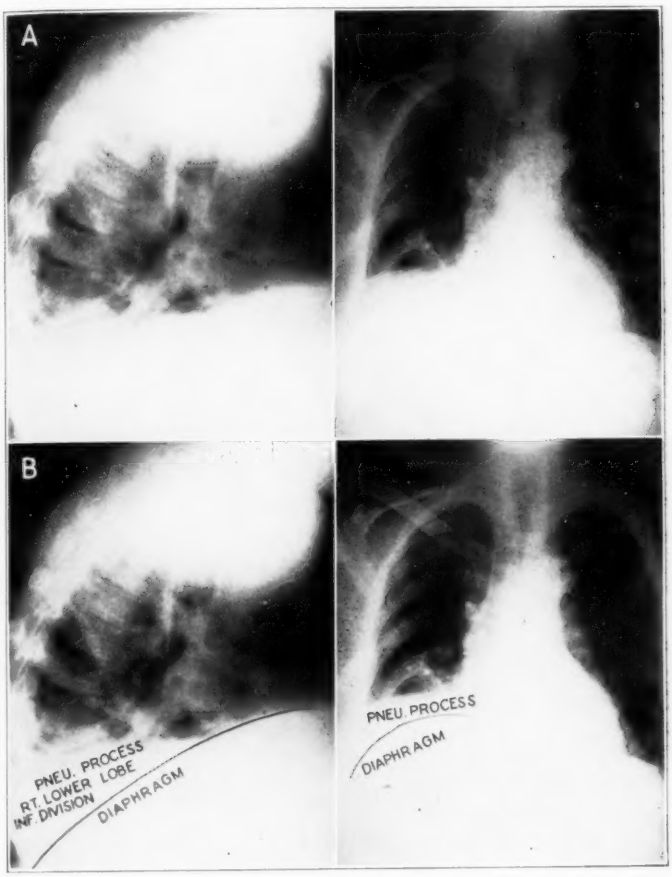


Fig. 10.—A pneumonic process involving the inferior division of the lower lobe of the right lung.

lying above, and continuous with, the shadow of the liver. In the lateral view most of the process is also masked by the shadow of the liver. An area of increased density occupies the part of the lung in the recess behind the diaphragm. This part of the lobe is frequently

involved by postoperative atelectasis. One may account for this fact by the action of gravity on the secretions in the bronchi when the patient is in the upright or semirecumbent position.

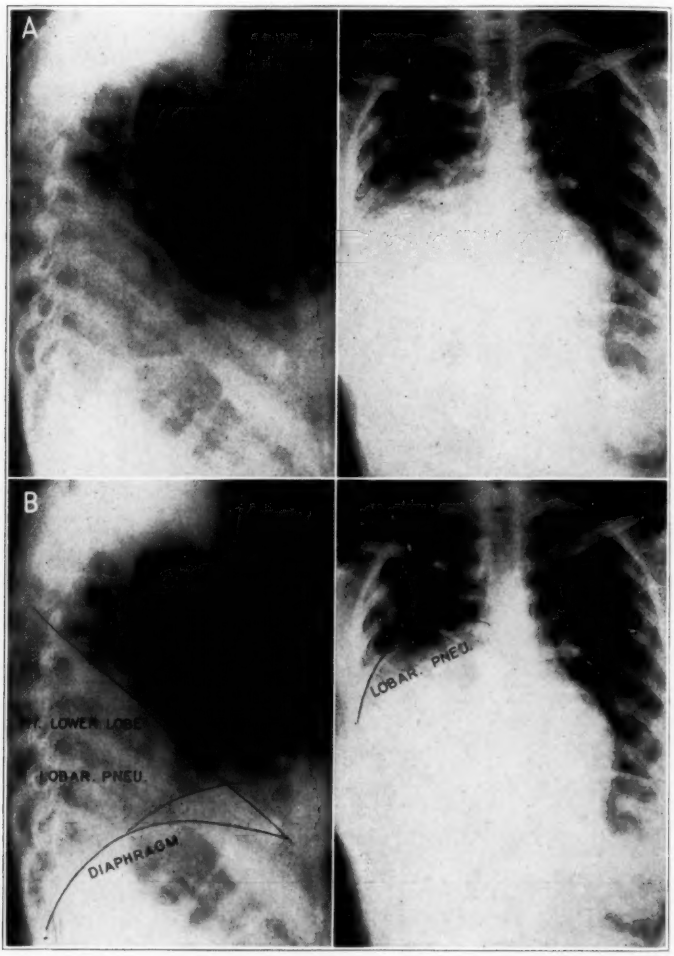


Fig. 11.—Lobar pneumonia involving the entire lower lobe (superior and inferior divisions) of the right lung.

The roentgenograms for case 5 (fig. 10), observed through the courtesy of Dr. L. C. Jacobs, illustrate the pneumonic process of the inferior division of the lower lobe.

The whole lobe, i. e., the superior and inferior divisions, may be involved by a pneumonic process. The shadow on the roentgenograms for case 6 is a combination of the shadows of involvement of the superior and the inferior division of the lower lobe.

CASE 6 (fig. 11; courtesy of Dr. F. Firestone).—P. H., a woman aged 25, had a sudden onset of chill, pain in the chest and cough. The temperature was 40 C. (104 F.), the pulse rate 120 and the respiratory rate 39. Physical examination revealed dulness of the lower lobe of the right lung, with bronchophony and tubular breathing. Roentgenograms showed an area of density involving the entire lower lobe. The diagnosis was lobar pneumonia. This was confirmed at autopsy.

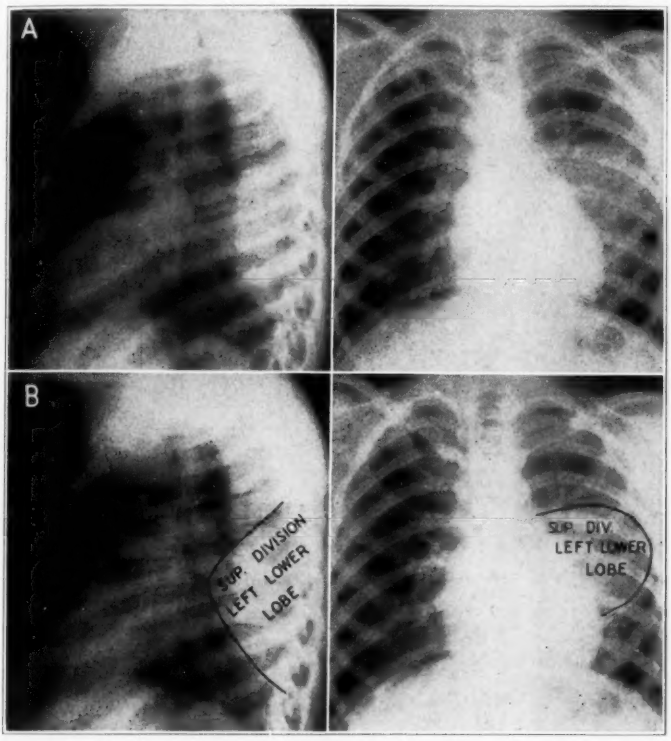


Fig. 12.—A pneumonic process involving the superior division of the lower lobe of the left lung.

The lower lobe of the left lung is as frequently involved by a disease process as the lower lobe of the right lung. The appearance on the roentgenogram is similar to that on the right side.

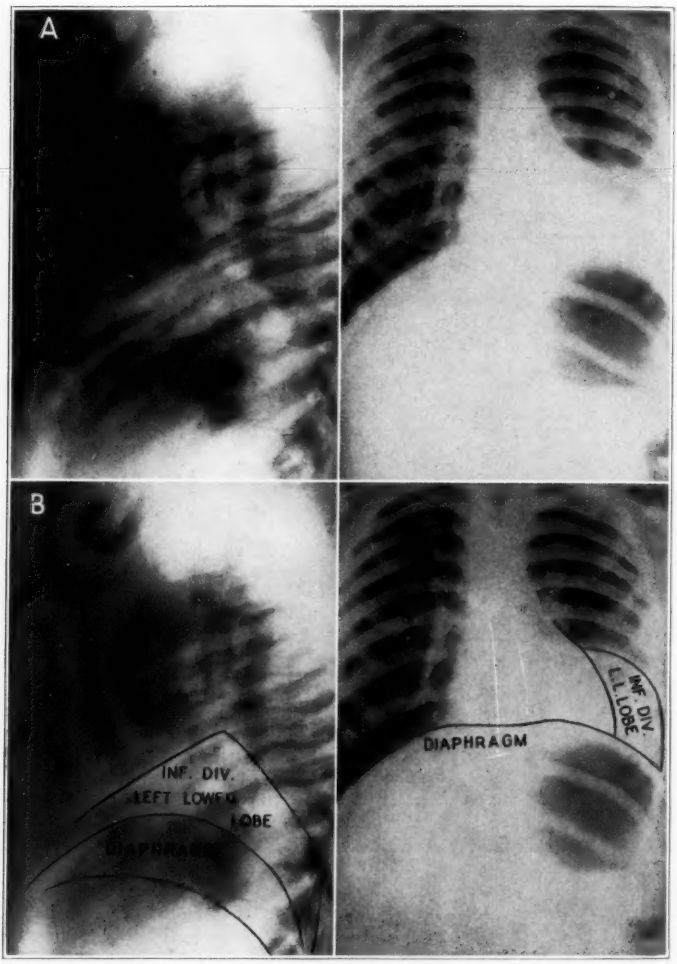


Fig. 13.—Atelectasis of the inferior division of the lower lobe of the left lung. The involved lung has a tented appearance. The diaphragm is elevated and extends to the superior division of the lower lobe. This aerated lung of the superior division may mask the physical signs of a collapsed lung.

The roentgenograms of the following cases illustrate disease processes in the lower lobe of the left lung.

CASE 7 (fig. 12; courtesy of Dr. G. J. Heppner).—A. S., a girl aged 7 years, had an onset of pain in the chest, with cough. The temperature was 105 F., the pulse rate 130, and the respiratory rate, 30. Physical examination revealed an area

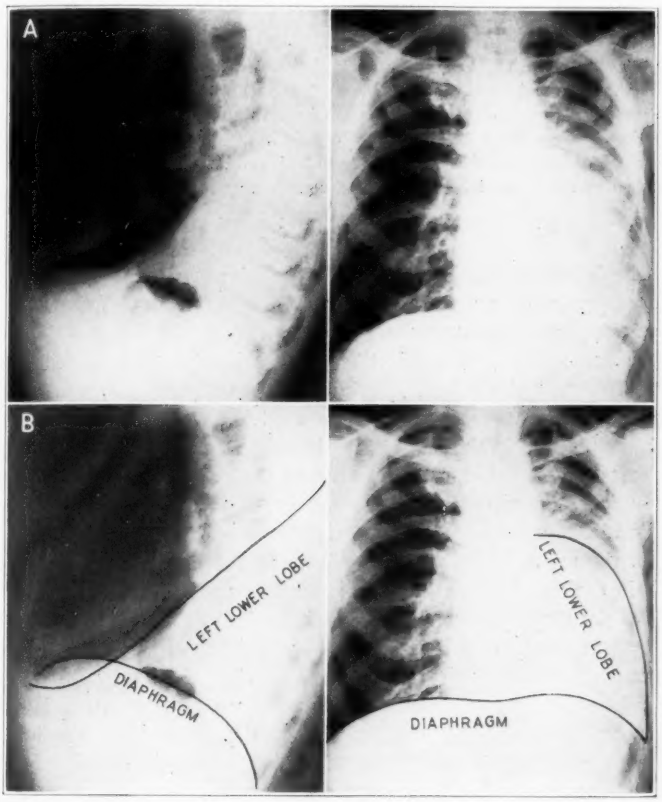


Fig. 14.—Atelectasis of the entire lower lobe (superior and inferior divisions) of the left lung.

of dulness on the left side posteriorly between the scapula and the spine. There were increased breath sounds and bronchial breathing. The diagnosis was pneumonia and was confirmed by the roentgenogram. The patient recovered. The process cleared in five days.

The roentgenograms for case 8 illustrate atelectasis of the inferior division of the lower lobe of the left lung.

Case 8 (fig. 13; courtesy of Dr. E. Wolff).—C. G., a boy aged 10 years, had an infection of the upper respiratory tract followed three weeks later by a nonproductive cough and a slight elevation of temperature to 99 F. Physical examination revealed dulness of the base of the left lung posteriorly, with absence of breath sounds. The diagnosis was atelectasis of the inferior division of the lower lobe of the left lung resulting from a plug of the bronchus by mucous secretions. The patient recovered, and the process in the lung cleared.

Case 9 illustrates atelectasis of the entire lower lobe of the left lung.

Case 9 (fig. 14; courtesy of Dr. L. H. Briggs).—J. O., a man aged 47, suffered from loss of weight and cough. Physical examination revealed emaciation and an area of dulness involving the left side of the chest posteriorly and in the axilla. A roentgenogram showed complete atelectasis of the lower lobe of the left lung. Bronchoscopic examination revealed bronchial carcinoma occluding the primary bronchus to the lower lobe of the left lung.

SUMMARY

The lower lobes of the right and left lungs are divided into two distinct parts: (1) a small triangular superior division and (2) a larger inferior division. This anatomic fact has been insufficiently emphasized in the past. Each portion of the lobe has its own bronchial distribution. Embryologically, each develops from a separate anlage. A fissure separating the two parts may be observed in the developed lung. The pleural reflection in the fissure may be noted in the roentgenogram and has often been misinterpreted as a pleural adhesion. This definite anatomic structure accounts for numerous limited disease processes the localization of which has previously not been understood.

In the roentgenogram the involved superior division appears to lie high in the chest or low behind the diaphragm, depending on the position of the diaphragm when the film is made. Failure to recognize the importance of the position of the diaphragm has often led to misinterpretations.

When the process appears high in the roentgenogram, it is often diagnosed as central pneumonia. When the process appears low on the roentgenogram, it may be mistaken for encapsulated fluid.

Note.—Since this article was submitted for publication, two other writers have noted a division of the lower lobe as involved by a disease process. Jönsson [4] demonstrated a separate bronchial division to these two parts and observed that silicotic changes occur most abundantly in the inferior part of the upper lobe and the superior part of the lower lobe; the inferior part of the lower lobe was not involved by silicosis.

4. Jönsson, C.: Some Roentgenological Observations Regarding Pulmonary Silicosis in Porcelain Workers, Acta Radiol. **16**:431, 1935.

Westermark [5] also demonstrated the two distinct bronchial divisions of these two portions of the lower lobe and demonstrated atelectasis as it occurred with tuberculosis as affecting either the superior or the inferior part of the lower lobe. Neither of the aforementioned writers demonstrated an anatomic or embryologic basis for this division.

Mr. J. Kelso, medical artist and photographer, made the reproductions of roentgenograms and the drawings.

516 Sutter Street.

384 Post Street.

5. Westermark, N.: Entwicklung und Vorkommen von Atelektase bei Lungentuberkulose, Acta Radiol. **16**:531, 1935.

FACTORS RESPONSIBLE FOR JAUNDICE IN SYPHILIS

WITH SPECIAL REFERENCE TO THE RÔLE OF THE ARSPHENAMINES

ROBERT V. SAGER, M.D.
NEW YORK

For at least four hundred years physicians have known of the occurrence of jaundice with syphilis (Paracelsus,[1] 1510). The introduction of arsphenamine seems to have increased the incidence and the complexity of this condition. Since in syphilis, as in any other disease, treatment is necessarily guided by the concepts of etiology, it is of paramount importance to determine the exact causes of the jaundice. To this end in the present study I proposed to investigate the factors concerned in the occurrence of jaundice with syphilis and to correlate them with recent acquisitions to the clinical, experimental and pathologic knowledge of disease of the liver.

In the discussion of this subject it is necessary at the outset to define certain terms and concepts that are employed. The term the arsphenamines is used to indicate the entire family of organic arsenical antisyphilitic preparations, all of which are associated with the condition herein discussed. It is clear from clinical experience and from the work of Luithlen [2] and others that the toxic actions of the arsphenamines, on the one hand, and those of its constituent parts per se—arsenic and benzene—on the other, are different. This is true quantitatively even more than qualitatively. The hepatotoxic power of the arsphenamines is incomparably greater than that of inorganic arsenic.

Benign nonobstructive jaundice and acute yellow atrophy occurring in untreated persons with syphilis in the secondary stage are called icterus syphiliticus praecox. The same complications of secondary and tertiary syphilis occurring while the patient is under treatment with the arsphenamines are called early icterus; if the jaundice appears within ten months after the cessation of treatment, it is called late icterus. Under the term paratherapeutic icterus are included both early and late

---

From the Medical Service of Dr. B. S. Oppenheimer, The Mount Sinai Hospital.

This study was aided by a grant made to the Emanuel Libman Fellowship Fund in memory of Theresa Backer.

1. Paracelsus, cited by Proksch, J. K.: Paracelsus über die venerischen Krankheiten und die Hydrargyrose, Med.-Chir. Centralbl. **17**:289, 313, 337, 361, 387, 411, 434 and 458, 1882.

2. Luithlen, F.: Die experimentelle Analyse der Salvarsanwirkung, Ztschr. f. Exper. Path. u. Therap. **13**:493, 1913.

icterus. Benign jaundice designates the condition in patients who make a complete recovery. Acute yellow atrophy is used for convenience to designate the condition in all fatal cases of jaundice in which it is proved pathologically to be acute, subacute or even chronic yellow atrophy, the last of which is more properly termed coarse nodular or toxic cirrhosis. It is obvious that in a case of jaundice with syphilis the diagnosis of paratherapeutic icterus cannot be made until all other types of jaundice are excluded, for instance, all hemolytic and obstructive types.

General confusion is fostered by an inadequate classification of the subject. Some authorities, for instance, have held that the cause of acute yellow atrophy following treatment with arsphenamine differs from that of benign paratherapeutic icterus (Kerl;[3] Herxheimer[4]); others have contended that early and late icterus are essentially different (Pulvermacher;[5] Wosegien[6]) and many have made complicated differentiations on decidedly questionable grounds.

Clinically, benign paratherapeutic jaundice simulates so-called catarrhal jaundice, which since the earliest observations (Chauffard;[7] Heitler[8]) has been recognized more and more clearly as a parenchymatous degenerative process in the liver. Since the number of fatal cases is usually far smaller than the number of cases of the benign variety, one may conclude that in the cases of the benign type the condition is acute or subacute yellow atrophy *en miniature* and differs from acute yellow atrophy only in severity. Indeed, Eppinger,[9] Klemperer, Killian and Heyd,[10] Wallgreen,[11] Huber and Kausch,[12] and Albot[13] were fortunately

3. Kerl, W.: Schädigungen durch Salvarsan, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 18.

4. Herxheimer, G.: Ueber akute gelbe Leberatrophie, Syphilis und Salvarsan, Berl. klin. Wchnschr. **57**:369 (April 19) 1920.

5. Pulvermacher, L.: Zur Frage des Spätikterus nach Salvarsan, Dermat. Ztschr. **27**:199, 1919; **24**:577 and 648, 1917.

6. Wosegien, H.: Ueber Ikterus nach Salvarsanbehandlung des Ikterus, Arch. f. Dermat. u. Syph. **1**:139, 1920.

7. Chauffard, A.: Contribution à l'étude de l'ictère catarrhal, Rev. de med. **5**:9, 1885.

8. Heitler, M.: Ueber Ikterus typhoïdes, Wien. Med. Wchnschr. **37**:958, 1887.

9. Eppinger, H.: Spezielle Pathologie des Ikterus, in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie innerer Krankheiten, Vienna, Urban & Schwarzenberg, 1923, vol. 6; Verhandl. d. deutsch. path. Gesellsch. **18**:272, 1921; Ueber Ikterus, Klin. Wchnschr. **1**:1182, 1922.

10. Klemperer, P.: Killian, J. A., and Heyd, C. G.: The Pathology of Catarrhal Icterus, Arch. Path. **2**:631 (Nov.) 1926.

11. Wallgreen, A.: An Epidemic of Catarrhal Jaundice, Acta med. Scandinav. (supp.) **26**:118, 1928.

12. Huber, O., and Kausch, W.: Zur Klinik der subakuten Leberatrophie, Berl. klin. Wchnschr. **57**:81, 1920.

13. Albot, G.: Hépatites et cirrhoses, Paris, Masson & Cie., 1931.

able to verify this observation in patients with catarrhal jaundice who had died by accident or who had had material from the liver subjected to biopsy. I have recently observed on postmortem examination the same condition in the liver of a patient recovering from paratherapeutic jaundice, who died of confluent bronchopneumonia (case 1). According to evidence derived from tests of hepatic function, identical parenchymatous damage occurs in cases of catarrhal jaundice, acute yellow atrophy and benign and fatal paratherapeutic jaundice, with only slight qualitative differences. This was emphasized by Geronné,[14] Strauss and Buerkmann,[15] Wolf,[16] Queyrat,[17] Lewin[18] and Kirch and Freundlich[19] and was also confirmed in the cases observed during the course of this study. It would, in fact, be as unreasonable to regard lobar pneumonia in cases with recovery as totally different from lobar pneumonia in fatal cases as to conceive a different pathologic process and pathogenesis for benign and fatal paratherapeutic icterus. Therefore, one may state that benign jaundice occurring in persons with syphilis represents the same condition as mild acute or subacute yellow atrophy. This does not deny that the condition in certain epidemics of catarrhal jaundice may be cholangeitis, as Cantacuzène[20] asserted. However, those who, like McDonald,[21] believe paratherapeutic jaundice to be infectious, usually incriminating bacteria of the colon-typhoid group, submit evidence depending on the results of postmortem cultures of the blood, bile and liver tissue. Without adequate controls these results are worthless, as shown by the studies of Epstein and Kugel.[22] Moreover, Libman[23] observed in cases of parenchymatous degeneration of

14. Geronné, A.: Zur Pathogenese einiger Formen des Ikterus (Ein Beitrag zur Frage des Leucins und Tyrosins), Klin. Wchnschr. **1**:828, 1922.

15. Strauss, L., and Buerkmann, W.: Der Einfluss des Salvarsans auf die Bilirubinreaktion im Blutserum bei Lueskranken, zugleich ein Beitrag zur Frage der Salvarsanschädigungen, Klin. Wchnschr. **1**:1407 (July 8) 1922.

16. Wolf, M.: Leberfunktion bei Lues und ihre Bedeutung zur Verhütung von Salvarsanschäden, Dermat. Ztschr. **42**:169, 1924.

17. Queyrat, M. L.: Salvarsan et néosalvarsan; de quelques réactions du foie consécutives à leur injection; meiopragie hépatique à type urobilinurique, Bull. et mém. Soc. méd. d. hôp. de Paris **38**:299, 1914.

18. Lewin, E. M.: Neues zur Lehre von der toxischen Wirkung der Arsenobenzolpräparate auf die Leber, Arch. f. Dermat. u. Syph. **159**:77, 1929.

19. Kirch, A., and Freundlich, J.: Zur Frage der Leberschädigung bei Lues und Salvarsantherapie, Arch. f. Dermat. u. Syph. **136**:107, 1921.

20. Cantacuzène, J.: Sur une épidemie d'ictère observée en Roumanie pendant la campagne de 1917, Presse méd. **26**:541, 1918.

21. McDonald, S.: Acute Yellow Atrophy in Syphilis, Brit. M. J. **1**:76, 1918.

22. Epstein, E. Z., and Kugel, M. A.: The Significance of Postmortem Bacteriological Examination, J. Lab. & Clin. Med. **44**:327, 1929.

23. Libman, E.: On Some Experiences with Blood Cultures in the Study of Bacterial Infections, Bull. Johns Hopkins Hosp. **17**:215, 1926.

the liver of unknown etiology that cultures of the blood made during life were sterile.

The purpose of the study reported here was to investigate the relation of arsphenamine therapy to jaundice. Thirty-one cases have been observed, and the literature has been studied.

RELATION OF DEFINITE ANATOMIC SYPHILIS OF THE LIVER TO JAUNDICE

Slight transient jaundice may be encountered in cases of syphilitic cirrhosis, but neither this condition nor gumma of the liver gives the familiar picture of benign or fatal jaundice. In my records there were twelve cases of gumma of the liver, syphilitic cirrhosis or hepar lobatum; in only one instance was jaundice present, and in that case it was faint and transient. Wile and Sams [24] reported similar observations.

A careful search of the records of the cases of tertiary syphilis of the liver with necropsy observations reported by Murchison,[25] Legg,[26] Fournier,[27] Frerichs,[28] McCrae and Caven [29] and other observers, both before and after the introduction of arsphenamine, failed to reveal in a single case a condition which will fit into the picture of acute yellow atrophy. Nor are the clinical pictures of the two diseases alike. On the other hand, lesions in cases of fatal paratherapeutic icterus are always those of acute or subacute yellow atrophy or coarse nodular cirrhosis; the familiar lesions of hepatic syphilis are uniformly absent, and spirochetes are never found, as pointed out by Ravaut [30] and Fischer [31] and as mentioned in the following section. Even if gumma or syphilitic cirrhosis should be found in association with acute yellow atrophy, the etiologic relation of the two would not thereby be proved. But I am aware of no case in which this association was present.

---

24. Wile, U. J., and Sams, W. M.: A Study of Jaundice in Syphilis: Its Relation to Therapy, Am. J. M. Sc. **187**:297 (March) 1934.

25. Murchison, C.: Clinical Lectures on Diseases of the Liver, London, Longmans, Green & Company, 1874.

26. Legg, J. W.: Bile, Jaundice, and Bilious Diseases, London, H. K. Lewis, 1880.

27. Fournier, A.: Traité de syphilis, Paris, J. Rueff, 1906, vol. 2, pt. 2.

28. Frerichs, F. T.: A Clinical Treatise of Diseases of the Liver, London, New Sydenham Society, 1860.

29. McCrae, T.: Tertiary Syphilis of the Liver, Am. J. M. Sc. **144**:625 (Nov.) 1912. McCrae, T., and Caven, W. R.: Tertiary Syphilis of the Liver, Am. J. M. Sc. **172**:781 (Dec.) 1926.

30. Ravaut, P.: Pathogenesis and Therapy of Para-Arsenical Icterus, Bull. Soc. franç. de dermat. et syph. **35**:818, 1928; in discussion, ibid. **35**:237 and 887, 1928; Ictère survenu deux mois après un traitement arsénicomercuriel: Ictère grave. Mort, ibid. **28**:57, 1921.

31. Fischer, B.: Ueber Todesfälle nach Salvarsan, Deutsche med. Wchnschr. **41**:908, 939 and 976, 1915.

Therefore, it can be definitely asserted that there is no proved relation between anatomic tertiary syphilis of the liver and paratherapeutic jaundice.

RÔLE OF THE ARSPHENAMINES IN THE CAUSATION OF JAUNDICE

1. Jaundice with Syphilis Before the Introduction of the Arsphenamines.—Only one type of frank jaundice was associated with syphilis in the prearsphenamine era. This occurred in the secondary stage only and was called icterus syphiliticus praecox. Though known since the sixteenth century, an accurate description of the syndrome with and without acute yellow atrophy was not made until the nineteenth century. Portal [32] and Ricord [33] vaguely delineated it; then Gubler [34] (1856), followed by Lancereaux [35] and Lasch,[36] more thoroughly described its characteristics. Lebert [37] and Engel-Reimers [38] noted the occurrence of acute yellow atrophy as a complication. According to Werner's [39] extensive statistics, the disease occurred in 0.37 per cent of persons with syphilis in the secondary stage.

Icterus syphiliticus praecox, as noted previously, is a nonobstructive type of jaundice. It usually appears at the same time as the eruptive phenomena of the secondary stage but may precede or follow them by a short interval. Symptoms may appear shortly after the inception of treatment with mercury or bismuth, since these drugs do not manifest their therapeutic action as quickly as the arsphenamines. The jaundice has occasionally been attributed to mercury, but there is no trustworthy evidence to substantiate this contention, as was pointed out long ago by Lebert [37] and more recently by Stokes and his associates.[40]

---

32. Portal, A.: Observations sur la nature et le traitement des maladies du foie, Paris, Longchamps, 1813.

33. Ricord, P.: Traité complet des maladies vénériennes, Paris, J. Rouvier, 1851.

34. Gubler, A.: Mémoire sur l'ictère qui accompagne les éruptions syphilitiques précoces, Compt. rend. Soc. de biol. (pt. 2) **5**:235, 1854.

35. Lancereaux, E.: A Treatise on Syphilis, London, New Sydenham Society, 1868.

36. Lasch, O.: Visceral Affections in the Early Stages of Syphilis: I. Icterus Syphiliticus Praecox, in Selected Essays and Monographs, London, New Sydenham Society, 1900, p. 145; Berl. Klin. Wchnschr. **31**:904, 1894.

37. Lebert: Ueber Ikterus typhoïdes, Virchows Arch. f. path. Anat. **7**:341, 1854-1855.

38. Engel-Reimers, J.: Akute gelbe Leberatrophie in der Frühperiode der Syphilis, Jahrb. d. Hamb. Straatskrankenanst. **1**:325, 1889.

39. Werner, S.: Beiträge zur Pathologie des Ikterus syphiliticus, München. med. Wchnschr. **44**:736, 1897.

40. Stokes, J. H.; Reudemann, R. J., and Lemon, W. S.: Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:521 (Nov.) 1920.

When insufficient treatment has been given jaundice may appear as part of a generalized secondary recurrence in association with the typical cutaneous and mucosal phenomena and a positive reaction to the Wassermann test—facts which must be emphasized. Gennerich,[41] Ruge[42] and Fuhs and Weltmann[43] reported many cases, all of which clearly establish these criteria for the recognition of icterus syphiliticus praecox as a complication of a recurrence of secondary syphilis following inadequate treatment.

The prognosis in cases of icterus syphiliticus praecox is generally good, the condition usually running the benign course of catarrhal jaundice. However, approximately 10 per cent of patients die of acute yellow atrophy (Engel-Reimers;[38] Weber[44]).

Investigation of postmortem material has thus far failed to reveal Spirochaeta pallida in the liver, although sections of the skin made simultaneously may have shown spirochetes in profusion (Fuhs and Weltmann;[43] Buraczynski;[45] Veszprémi and Kanitz;[46] Schmorl;[47] Buschke and Michael;[48] Bierring;[49] Severin and Heinrichsdorff;[50] Herxheimer and Gerlach[51]). Inoculations of hepatic tissue into animals have likewise given negative results. Only Warthin[52] succeeded in demonstrating spirochetes in the liver of a patient with icterus syphiliti-

41. Gennerich, W.: Der Behandlung der Syphilis mit Salversanpräparaten, Ergebn. d. inn. med. u. Kinderh. **20**:368, 1921.

42. Ruge, H.: Zehn Jahre Gelbsucht in der Marine (1919-1929), Beobachtungen an 2,500 Fällen, Ergbn. d. inn. Med. u. Kinderh. **41**:1, 1931.

43. Fuhs, H., and Weltmann, O.: Ueber Ikterus bei Lues, Arch. f. Dermat. u. Syph. **140**:247, 1922.

44. Weber, F. P.: Acute Hepatic Atrophy in Early or Secondary Syphilis, Proc. Roy. Soc. Med. (Path. Sect.) **2**:116, 1909.

45. Buraczynski, A.: Ikterus im Frühstadium der Lues, Wien. klin. Rundschau **21**:651, 1907.

46. Veszprémi, D., and Kanitz, H.: Akute gelbe Atrophy bei Lues 2, Arch. f. Dermat. u. Syph. **88**:35, 1907.

47. Schmorl: Pathologic Demonstrations, München. med. Wchnschr. **69**:908, 1922.

48. Buschke, A., and Michael: Salvarsanwirkungen, Berl. klin. Wchnschr. **51**:1935, 1914.

49. Bierring, K.: Tötliche Lebersyphilis, Zentralbl. f. Haut- u. Geschlechtskr. **7**:411, 1922.

50. Severin and Heinrichsdorff: Zur Frage der Leberveränderungen nach Salvarsan, Ztschr. f. klin. Med. **76**:128, 1912.

51. Herxheimer, G., and Gerlach, W.: Ueber Leberatrophie und ihre Verhältnisse zu Syphilis und Salvarsan, Beitr. z. path. Anat. u. z. allg. Path. **68**:93, 1921.

52. Warthin, A. S.: The New Pathology of Syphilis, Am. J. Syph. & Neurol. **2**:425, 1918.

cus praecox (one case). However, his report lacks detail, and his observations are at variance with those of all other investigators in the field.

The conclusion, therefore, is strongly suggested that the jaundice in untreated persons with secondary syphilis is caused by parenchymatous hepatic injury effected indirectly by the spirochete through the toxemia associated with its generalization and that it is not caused by an inflammatory reaction of the liver to the spirochete itself. Most of the investigators cited earlier agreed with this conception. It is also in accord with the demonstration by Babalian,[53] Sade,[54] Kleeberg,[55] Kirch and Freundlich [19] and others that tests of function reveal hepatic damage in a considerable proportion of cases of secondary syphilis without jaundice.

2. Comparison of Incidence of Jaundice with Syphilis Before and After the Introduction of Arsphenamine.—With the era introduced by Ehrlich in 1910, jaundice as a complication of syphilis or its treatment assumed significant proportions not only in the secondary but also in the tertiary stage of the disease. Although paratherapeutic icterus did not gain wide notice in Europe until the period of the World War and in America until later, the number of cases reported before the war was considerable. The first cases were described in 1910. Dujardin,[56] of Brussels, in January 1914 stated that he had observed twenty-five cases following the use of neoarsphenamine. Jaundice, which before the introduction of arsphenamine had been estimated as a complication in 0.37 per cent of the cases of secondary syphilis and in none of the cases of tertiary syphilis, was now a frequent occurrence in both phases of the disease. Reports from almost every country show a considerable incidence of paratherapeutic icterus. Cole and his associates [57] in the United States estimated it at about 2 per cent of cases in which treatment had been given, and Scott and Pearson [58] in Canada estimated it

53. Babalian: Les rétentions biliaires latentes des syphilitiques, Bull. Soc. franç. de dermat. et syph. **35**:870, 1928.

54. Sade, I.: Die Leberfunktionprüfungen bei Syphilis und Salvarsanikterus, Zentralbl. f. Haut- u. Geschlechtskr. **23**:62, 1927.

55. Kleeberg, L.: Ueber Leberfunctionsprüfungen bei Lues, Med. Klin. **16**: 1162, 1920.

56. Dujardin, B.: Les ictères toxiques dûs au néo-salvarsan, Clinique, Brussels **28**:103, 1914.

57. Cole, H. N.; De Wolf, H.; McCluskey, J. M.; Miskjian, H. F.; Williamson, G. S.; Rauschkolb, G. R.; Ruch, R. O., and Taliaferro, C.: Toxic Effects Following Use of the Arsphenamines, J. A. M. A. **97**:897 (Sept. 26) 1931.

58. Scott, G. O., and Pearson, G. H. J.: A Preliminary Report on Syphilitic and Arsenical Jaundice, Am. J. Syph. & Neurol. **3**:628, 1919.

at about the same figure. Other estimates were as follows: Filliol [59] in France, 7.7 per cent; Milian and his co-workers,[60] about 20 per cent; Ruge [42] (incidence in the German marine corps), about 19 per cent; Gutmann,[61] 7.4 per cent; Gerrard [62] (incidence in the British navy), 4.6 per cent; Gorodetzky and Nartzissoff [63] in Russia, 2.5 per cent, and Gjessing [64] in Sweden, 1 per cent.

It is particularly illuminating to compare McCrae's [29] 1912 and 1926 reports on tertiary syphilis of the liver. While in the former there was no mention of a case in which the conditions simulated catarrhal jaundice, in the latter it was necessary to specify that such cases had been excluded because the patients had all received arsphenamine. A similar impression is obtained from the reports of MacLean,[65] McDonagh,[66] McDonald,[21] Gottron,[67] Brocq [68] and O'Leary, Greene and Rowntree.[69] Another change was noted by Heinrichsdorff [70] in the incidence according to sex. Previously icterus syphiliticus praecox had been predominant in females by two to one. Paratherapeutic icterus, however, usually predominates in males.

These changes, which directly followed the introduction of arsphenamine in the frequency and the character of involvements of the liver in persons with syphilis, are so striking and definite that only arsphenamine can be held responsible for them.

3. Experimental Evidence of the Hepatotoxic Action of the Arsphenamines.—Arsenic may be demonstrated in the liver and in the

59. Filliol, L.: Les ictères au cours de traitements arsénobenzoliques, Arch. dermat.-syph. de clin. de l'hôp. St. Louis **2**:597, 1930.

60. Milian, G.; Lotte, and Delarue: L'ictère parathérapeutique, Bull. Soc. franç. de dermat. et syph. **35**:873, 1928.

61. Gutmann, C.: Erfahrungen über Ikterus bei Syphilitikern, Dermat. Ztschr. **37**:39, 1922.

62. Gerrard, W. I.: The Recognition of Latent Jaundice During Treatment with Arsenobenzol Compounds, Brit. M. J. **2**:224, 1924.

63. Gorodetzky, A., and Nartzissoff: Course and Diagnosis of Late Arsphenamine Jaundice, Venerol. dermat. **7**:25, 1930.

64. Gjessing, H. C.: Syphilis, Salvarsan, and Paratherapeutic Jaundice, Acta dermat. venerol. **11**:479, 1930.

65. MacLean, H.: Arsenobenzol Treatment of Syphilis, Brit. M. J. **2**:944, 1921.

66. McDonagh, J. E. R.: Acute Yellow Atrophy in Lues, Brit. M. J. **1**:189, 1918.

67. Gottron: Akute gelbe Leberatrophie bei mit Salvarsan behandelten Syphilitikern, Dermat. Ztschr. **35**:300, 1921-1922; **36**:225, 1922.

68. Brocq, L.: Syphilitiques traités par les injections intraveneuses des nouveaux composés arsénicaux, Bull. méd., Paris **35**:235, 1921.

69. O'Leary, P.; Greene, C. H., and Rowntree, L.: Diseases of the Liver: Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function, Arch. Int. Med. **44**:155 (Aug.) 1929.

70. Heinrichsdorff: Leber-Lues, Salvarsan, Virchows Arch. f. path. Anat. **240**: 441, 1922-1923.

urine of both man and animals after an injection of arsphenamine, as many observers (Wilcox;[71] Ullmann;[72] Policard and Pinard;[73] Tachau,[74] Morel and his co-workers[75]) have demonstrated. However, since arsenic may also be observed in the liver of a person in whom jaundice does not develop, even though treated with arsphenamine, these facts are not of striking significance.

On the other hand, laboratory animals suffer from focal hepatic necrosis and often from functional impairment when an arsphenamine preparation is injected. This has been repeatedly demonstrated by Voegtlin,[76] Hooper and his associates,[77] Morel and his associates,[75] Kolmer and Lucke[78] and others. Jaundice in animals has been difficult to induce, but Kolle,[79] Hooper,[77] Craven[80] and Schifrin[81] succeeded in doing so by administering huge doses of arsphenamine to dogs.

4. Relation of the Incidence of Jaundice to the Quantity of the Drug Given.—The relation of the quantity of a drug administered to the effect produced is usually difficult to demonstrate, because idiosyn-

71. Wilcox, W. A.: Arsenobenzol Treatment of Syphilis, Brit. M. J. **2**:944, 1921; Lancet **1**:869, 1919.

72. Ullmann, K.: Ueber Ausscheidungswerte und Speicherungsverhältnisse nach Einfuhr von Salvarsan in dem menschlich-tierschen Organismus, Arch. f. Dermat. u. Syph. **114**:511, 1912.

73. Policard, A., and Pinard, J.: A propos de la question des ictères au cours du traitement arsénical de la syphilis: Un cas d'ictère grave mortel avec dosage de l'arsénic dans le foie, Paris méd. **39**:42, 1921.

74. Tachau: Zur Kritik des Salvarsanikterus, Deutsche med. Wchnschr. **47**: 677, 1921.

75. Morel, A.: Mouriquand, G., and Policard, A.: Le "606," le foie, et le rein, Lyon méd. **118**:1340, 1912; Bull. et mém. Soc. méd. d. hôp. de Paris **37**:402, 1914.

76. Voegtlin, C.: The Pharmacology of Arsphenamine and Related Arsenicals, Phys. Rev. **5**:63, 1925.

77. Hooper, C. W.; Kolls, A. C., and Wright, K. D.: The Influence of Fasting, and Various Diets on Arsphenamine Poisoning, and the Comparative Toxicity of Arsphenamine, Neoarsphenamine and Paraoxyaminophenylarsenoxide, J. Pharmacol. & Exper. Therap. **18**:133, 1921.

78. Kolmer, J. A., and Lucke, B.: A Study of the Histological Changes Produced Experimentally in Rabbits by Arsphenamine, Arch. Dermat. & Syph. **3**:483 (April) 1921; A Study of the Histologic Changes Produced Experimentally in Rabbits by Neoarsphenamine, ibid. **3**:515 (April) 1921; A Study of the Histologic Changes Produced Experimentally in Rabbits by Mercurial Compounds, ibid. **3**: 531 (April) 1921.

79. Kolle, W.: Experimentelle Studien zu Ehrlichs Salvarsantherapie der Spirochätenkrankheiten und über neue Salvarsanpräparate, Deutsche med. Wchnschr. **44**:1177 and 1211, 1918.

80. Craven, E. B., Jr.: Importance of Diet in Preventing Acute Yellow Atrophy During Arsphenamine Treatment, Bull. Johns Hopkins Hosp. **48**:131 (March) 1931.

81. Schifrin, A.: Der Einfluss qualitativ verschiedener Ernährungsformen auf die durch Salvarsan hervorgerufene Lebernekrose, Virchows Arch. f. path. Anat. **287**:175, 1932.

crasy (using this term in its widest sense) may be involved. For instance, Biele,[82] Taege[83] and Weigeldt[84] reported cases in which a huge single or total dose of arsphenamine was given without producing jaundice. On the other hand, Hyman[85] and Lane[86] reported cases in which jaundice occurred after a single conservative dose. Nevertheless, Bodin,[87] Brodier[88] and Laurent[89] were able to show in large series of cases that the incidence of jaundice varied directly with the size of the dose. Arndt,[90] Friedmann,[91] Heller[92] and other syphilologists have reported a decrease in the incidence of jaundice following a reduction of the size of the routine dose. Recently the highest incidence has been reported from France, where, in general, vigorous treatment is practiced.

Simon[93] attributed the jaundice to excessively toxic batches of the drugs. But the fact that jaundice has occurred so universally with all brands and with numerous separate batches of the same brand is a strong argument against the assumption that faulty manufacture of the drug plays a considerable rôle.

5. Association of Jaundice with Other Toxic Manifestations of the Arsphenamines.—An objection often leveled against the theory of the toxic etiology of paratherapeutic icterus is the frequent absence of other toxic reactions to arsphenamine. That such additional reactions may be absent is not surprising, since one seldom sees multiple toxic effects associated with arsphenamine dermatitis or with encephalitis associated

82. Biele, K.: Zur Dosierung des Salvarsans, Deutsche Med. Wchnschr. **47:** 619 (June 2) 1921.

83. Taege, K.: Zur Giftigkeit des Salvarsans, München. med. Wchnschr. **67:** 606, 1920.

84. Weigeldt, W.: Zur Dosierung des Salvarsan, Deutsche med. Wchnschr. **46:**1193, 1920.

85. Hyman, A. S.: Fatal Postarsphenamine Jaundice, New York M. J. **112:** 496, 1920.

86. Lane, J. E.: Discussion on Recent Developments in the Recognition and Treatment of Syphilis, Brit. M. J. **2:**673, 1911.

87. Bodin, E.: Les ictères par le néosalvarsan, Bull. Soc. franç. de dermat. et syph. **28:**242, 1921.

88. Brodier, L.: Note sur l'ictère de l'arsénobenzol, Ann. d. mal. vén. **15:** 465, 1920.

89. Laurent, C.: Les ictères des syphilitiques traités par le novarsénobenzol, J. d. méd. de Lyon **2:**1367, 1921.

90. Arndt: Salvarsanfrage, Med. Klin. **18:**231, 1922.

91. Friedmann, M.: Ueber Gelbsucht bei Syphilis während der Neosalvarsanbehandlung, Dermat. Ztschr. **26:**317, 1918.

92. Heller, J., in discussion on Gottron.[67]

93. Simon, C., in discussion on Sezary, M.: Apropos de la pathogénie et du traitement des ictères paraarsénicaux, Bull. Soc. franç. de dermat. et syph. **35:** 883, 1928.

with arsphenamine therapy and since sensitivity of one tissue or organ without a reaction on the part of the others is observed in many other fields of medicine.

Nevertheless, the number of cases of multiple toxic phenomena observed is considerable. Arsphenamine dermatitis is the most common toxic accompaniment of jaundice; but aplastic anemia, agranulocytic, leukopenic and monocytic reactions of the hematopoietic system and polyneuritis are not rare. Among my cases was one of monocytic angina, previously reported by Rosenthal,[94] and one of secondary anemia and leukopenia. Cole and his associates [57] reported two cases in which the condition was complicated by arsphenamine dermatitis, in one of which aplastic anemia also occurred. The literature contains many reports of cases with dual toxic phenomena.

6. Jaundice in Nonsyphilitic Patients Treated with the Arsphenamines.—It is not uncommon to encounter jaundice as a complication of the treatment of nonsyphilitic diseases with arsphenamine. Filliol [59] put the figure at 1.75 per cent. I have records of three such accidents —one in a case of chronic iritis, one in a case of multiple sclerosis and the third as the result of specific treatment in a case of syphilophobia. Sicard and his collaborators,[95] who first described paratherapeutic icterus without syphilis, reported two such cases. Bernheim,[96] Lindstedt,[97] Nast [98] and others have also reported cases. Ruge [42] reported fifty-two cases; however, many of his patients suffered from malaria or other diseases that might possibly be associated with jaundice.

The possibility that the condition in these cases may have represented intercurrent attacks of catarrhal jaundice will be discussed later. The assumption, however, is strongly indicated that arsphenamine was the sole cause.

7. Relation of Jaundice Following Treatment with the Arsphenamines to Active Syphilis of the Liver, the Herxheimer Reaction and So-Called Hepatorecurrences.—Concerning the jaundice occurring during the active treatment of syphilis with the arsphenamines (early icterus), there is ample reason to exclude syphilis as the cause. It is hardly credible that syphilitic involvement of the liver should progress

94. Rosenthal, N.: Leucopenic Infectious Monocytosis, in Libman Anniversary Volumes, New York, International Press, 1932, vol. 3, p. 1003.

95. Sicard, Haguenau and Kudelski: Traitement de la syphilis nerveuse chronique: Les éléments de contrôle de la médication novarsénicale, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:833, 1919.

96. Bernheim, E.: Syphilis- Ikterus- Salvarsans, Deutsche Med. Wchnschr. **51**:904 (March 29) 1925.

97. Lindstedt, F.: Ueber "Salvarsan Ikterus" und dessen Verhältnisse zum "katarrhalischen" und syphilitischen Ikterus, Acta med. Scandinav. **59**:209, 1923.

98. Nast, in discussion, Dermat. Wchnschr. **69**:505, 1919.

under treatment with arsphenamine while other syphilitic phenomena disappear. Furthermore, many patients already have a negative Wassermann reaction by the time the jaundice appears.

Some physicians regard the rare reaction which follows the first or second injection as a Herxheimer reaction; but even here, the considerations just mentioned, as well as the fact that spirochetes have never been demonstrated in the livers of patients dying of arsphenamine jaundice, make this seem improbable. Milian's concept of biotropism, i. e., that bactericidal drugs may somehow enhance the virulence of localized organisms, is too speculative to be accepted without further evidence.

Jaundice occurring after a lapse of treatment with the arsphenamines (late icterus) has been regarded by many as a recurrence of active syphilis affecting the liver only (so-called hepatorecurrence or monohepatorecurrence). The evidence against this conception is overwhelming. One finds that the patients have almost uniformly received adequate treatment; the reaction to the Wassermann test is often negative, and the jaundice never has been reported as occurring with manifestations of active syphilis. Indeed, Gennerich [41] stated pointedly that an isolated syphilitic hepatorecurrence is never encountered. He insisted, with justice, that the last organ to give evidence of a syphilitic relapse is the liver, and that when this involvement of the liver does occur there are always a well marked exanthem, a positive Wassermann reaction and a history of insufficient treatment. The condition in these cases is therefore to be considered as icterus syphiliticus praecox. The condition in all of Ruge's [42] and Fuhs' and Weltmann's [43] cases conformed to this formula. As for the so-called hepatorecurrences in cases of tertiary syphilis, one would hardly expect to see a relapse from the tertiary into the secondary stage. Moreover, Gutmann [61] did not encounter a single case of late icterus with any evidence of active syphilis in a series of seventy-five cases.

Paratherapeutic icterus, therefore, cannot be considered as a manifestation of active syphilis of the liver in any form, recurrent or otherwise.

8. Certain Arguments Usually Brought Against the Arsphenamine Etiology of Jaundice.—Latent Period Associated with Late Icterus: (*a*) Time relationships. One of the chief obstacles to the acceptance of late icterus as a product of the toxicity of arsphenamine is the difficulty in believing that a drug could cause its toxic manifestation long after the last dose was given. The opinion that it is an active syphilitic hepatorecurrence has already been discussed. Another view often maintained is that late icterus is merely catarrhal jaundice, which has accidentally attacked a syphilitic patient who has been treated with the arsphenamines. The chronological curve of the incidence of late icterus,

as shown by many long series of cases, reaches a peak from the fourth to the eighth week after the last antisyphilitic injection and then falls off to the ninth or tenth month. If late icterus were, in truth, accidental catarrhal jaundice, there would be just as many cases occurring twenty months after the last injection as two months after. Probably only the few scattered cases of jaundice that do occur after the tenth month are fortuitous cases of catarrhal jaundice. This definite curve of incidence therefore indicates a real relationship between late icterus and the previous administration of arsphenamine.

Late icterus, it should be noted, represents as much as 70 per cent of the cases of paratherapeutic jaundice (Ruge). In the small series of cases analyzed here it constituted 50 per cent.

(*b*) Studies of hepatic function. Although it is difficult to trace the course of hepatic degeneration by tests of the function of the liver, if judiciously studied the results do not fail to bring important, even if limited, indications that the injection of arsphenamine may be followed by hepatic damage even when jaundice is not produced. Wallis,[99] using the test for lipase in the blood, which according to the early work of Quinan[100] and Whipple[101] (1913) seems to be well founded, was able to show that after arsphenamine therapy, even though jaundice was not produced, functional damage to the liver reached its maximum about two months after the last injection. The damage gradually receded to normal at about the sixth month after the injections were stopped. Wallis confirmed these results with the levulose tolerance test. Similar results were also obtained with Widal's hemoclastic crisis, which, however, is a test the reliability of which has been seriously questioned.

This evidence may be correlated with the work of Chargin and Orgel,[102] who observed the level of bilirubin in the blood during and after arsphenamine therapy. Of eighty-two patients, fourteen showed an elevation of the level of bilirubin in the blood in the absence of frank clinical jaundice, the elevation appearing from three to five weeks after the last injection of arsphenamine. Kloeppel[103] and Schneider confirmed these results. Indeed, it is known that severe degenerative hepatic disease may be present and may even cause death without the

99. Wallis, R. L. M.: Brit. M. J. **2**:944, 1921.

100. Quinan, C.: Lipase Studies, J. M. Research **32**:45 and 73, 1915.

101. Whipple, G. H.: A Test for Hepatic Injury: Blood Lipase, Bull. Johns Hopkins Hosp. **24**:357, 1913.

102. Chargin, L., and Orgel, S. Z.: Jaundice in Syphilitic Persons Receiving Arsenical Medication: Its Early Detection and Possible Prevention, Arch. Dermat. & Syph. **7**:495 (April) 1923.

103. Kloeppel, F. W.: Lues und Salvarsan in ihrem ätiologischen Zusammenhang mit Icterus und Bilirubinämia, Klin. Wchnschr. **1**:2021 (Sept.) 1922; Dermat. Ztschr. **37**:137, 1922.

appearance of jaundice (Bergstrand,[104] Rolleston and McNee[105]). A case described by Stewart, Vining and Bibby[106] illustrates this fact: A girl, who was said to have had faint jaundice for two days after an injection of arsphenamine, died suddenly during a minor operation. This took place three months after the last injection of arsphenamine, and at the time of death there was no jaundice. Necropsy showed acute yellow atrophy.

The considerations already enumerated point to the existence of latent demage to the liver after treatment with arsphenamine in a considerable percentage of cases, even in the absence of jaundice.

(*c*) Analogy to the other hepatotoxins. Analogy may serve further to mitigate one's incredulity, since delayed jaundice is not produced only by arsphenamine but may be caused by other hepatotoxins as well. Tri-nitrotoluene, acetylene-tetra-chloride, di-nitrophenol and blue cross gas (di-phenylchlorarsine) have produced late icterus. The number of cases of tri-nitrotoluene poisoning that occurred several months after the victims had severed all connections with munitions factories is fairly large. Also, experimentally, Mallory and Parker[107] noted that in cases of acute copper poisoning the maximal hepatic damage does not appear immediately but is delayed more than two weeks.

Thus, the definite time relationship, the evidence of functional tests and the analogy to other hepatotoxins point to the etiologic importance of the arsphenamines in cases of late icterus.

Disappearance of Jaundice Following the Use of Arsphenamine While More Arsphenamine Is Being Given: (*a*) Analogy drawn from experimental pathologic changes in the liver. The most impregnable defense of those who have asserted the syphilitic etiology of arsphenamine jaundice is the fact that the jaundice may disappear during the continued administration of arsphenamine, a point stressed particularly by Milian, Lotte and Delarue,[57] Wosegien,[6] Fabry[108] and their followers, who assumed that thereby the syphilis of the liver was cured. Many have expressed the opinion that this argument is false, since it is well known that the patient also recovers without any antisyphilitic treatment. An adequate explanation of this paradox has not yet been advanced.

104. Bergstrand, H.: Ueber die akute und chronische gelbe Leberatrophie mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, Leipzig, Georg Thieme, 1930.

105. Rolleston, H., and McNee, J. W.: Diseases of the Liver, Gall Bladder and Bile Ducts, New York, The Macmillan Company, 1929.

106. Stewart, M. J.; Vining, C. W., and Bibby, J. P.: Subacute Yellow Atrophy in a Case of Syphilis Following Treatment with Galyl, J. Path. & Bact. **23**:120, 1919.

107. Mallory, F. B., and Parker, F., Jr.: Experimental Copper Poisoning, Am. J. Path. **7**:351 (July) 1931.

108. Fabry, H.: Spätikterus nach Salvarsan, Med. Klin. **14**:260, 1918.

Nevertheless, there are certain observations on the experimental pathologic changes of the liver which yield suggestive intimations of the mechanism of this paradoxical disappearance of arsphenamine jaundice under continued specific therapy. Anderson [109] and Lacquet,[110] co-workers of F. C. Mann, performed partial hepatectomy on rats and observed that the newly regenerated hepatic tissue was less easily and less extensively damaged by chloroform and carbon tetra-chloride than the normal liver. This observation is of the utmost significance, for postmortem examinations have shown that acute yellow atrophy without some evidence of regeneration and hyperplasia of the liver is uncommon. Therefore, when one gives arsphenamine to a patient with paratherapeutic icterus, the drug meets not only the same liver tissue that was present on previous injections but a regenerating or newly regenerated tissue different in many respects from its parent tissue—different in the content of glycogen, fat and protein (Hashimoto and Pick [111]), different in its reactive potentialities and different perhaps in its sensitivity (Rössle [112]). That this regeneration actually occurs was seen clearly in case 1, in which death occurred accidentally during the healing stage of paratherapeutic icterus.

The experimental observations of Opie and Alford,[113] Quinan [109] and Davis and Whipple [114] support the theory just mentioned. These authors found that animals surviving the administration of hepatic poison could be given equally large doses of the poison shortly afterward without increasing the necrosis of the liver. Ogata,[115] using icterogen,

---

109. Anderson, R. M.: Experimental Pathology of the Liver: II. Effect of Chloroform on the Normal and on the Restored Liver Following Partial Removal, Arch. Path. **14**:335 (Sept.) 1932.

110. Lacquet, A. M.: Effects of Carbon Tetrachloride on the Normal and on the Restored Liver After Partial Hepatectomy, Arch. Path. **14**:164 (Aug.) 1932.

111. Hashimoto, M., and Pick, E. P.: Ueber den intravitalen Eiweissabbau in der Leber sensibilisierter Tiere und dessen Beeinflussung der Milz, Arch. f. exper. Path. u. Pharmakol. **76**:89, 1914.

112. Rössle, R.: Allergie und Pathergie, Klin. Wchnschr. **12**:574 (April 15) 1933.

113. Opie, E. L., and Alford, L. B.: The Influence of Diet on the Toxicity of Substances Which Produce Lesions in the Liver and Kidney, J. A. M. A. **62**: 895 (March 21) 1914. Opie, E. L.; Barker, B. I., and Dochez, A. R.: Change in the Proteolytic Enzymes and Anti-Enzymes of the Blood Serum Produced by Substances (Chloroform and Phosphorus) Which Cause Degenerative Changes in the Liver, J. Exper. Med. **13**:162, 1911.

114. Davis, N. C., and Whipple, H. G.: Effect of Fasting and Various Diets on Liver Injuries Effected by Chloroform Poisoning, Arch. Int. Med. **23**:612 (May) 1919.

115. Ogata, T.: Beiträge zur experimentell erzeugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung der Gallencapillaren bei der Unterbindung des Ductus choledochus und der Ikterogenvergiftung, Beitr. z. path. Anat. u. z. allg. Path. **55**:236, 1913.

a powerful hepatotoxic organic arsenical preparation, noted that surviving poisoned rats, even while jaundiced, were unaffected by repeated injections of ordinarily lethal doses of the same poison. Schifrin,[81] in experiments with sodium arsphenamine, observed that in a dog in which jaundice had developed icterus did not recur when a larger dose was given one week later. Thus, it is evident that in animals under control conditions, even with arsphenamine poisoning, phenomena occur which are analogous to the paradoxical innocuousness of arsphenamine used in the treatment of paratherapeutic jaundice.

That young cells may be more resistant to hepatic poisons was also indicated by the work of Whipple[116] (1912). He noted that the livers of young pups were resistant to chloroform poisoning. This was later attributed by Graham[117] to the high glycogen content of their livers.

It must also be noted that Love,[118] another co-worker of Mann, obtained results contrary to those of Anderson and Lacquet. Using phosphorus instead of chloroform and carbon tetra-chloride, he found that phosphorus damaged the regenerated tissue more than the normal tissue. This observation neither denied the results of Anderson and Lacquet, who used chloroform and carbon tetra-chloride, nor destroyed my analogy, but it did emphasize the complexity of hepatic reactions. The explanation of these atypical reactions is probably connected with the fact that phosphorus causes fatty changes and necrosis in the periphery of the liver lobule, while chloroform, carbon tetra-chloride and the arsphenamines which cause acute yellow atrophy, destroy chiefly the central and middle portions of the lobule.

(*b*) Untoward accidents and recurrences of the jaundice. The mechanism just described is not always sufficient to protect the liver from the toxic effects of further treatment with arsphenamine. Contrary to the many reports of Milian, one may not recklessly continue the injection of arsphenamine in cases of paratherapeutic jaundice. Not only have a number of deaths occurred after such procedure but patients who had been doing well on nonspecific therapy have had a relapse on the resumption of treatment with arsphenamine. Milian and his associates,[60] reported that in four of ninety-three cases of paratherapeutic icterus in which neoarsphenamine was administered there were fatal results, which they attributed vaguely to certain accidental factors. The condition in Ravaut's[30] cases was more definite.

116. Whipple, G. H.: Insusceptibility of Pups to Chloroform Poisoning During the First Three Weeks of Life, J. Exper. Med. **15**:259, 1912.

117. Graham, E. A.: Resistance of Pups to Late Chloroform Poisoning in Its Relation to Glycogen, J. Exper. Med. **21**:185, 1915.

118. Love, J. G.: The Effect of Phosphorus on the Normal and on the Restored Liver Following Partial Hepatectomy, Arch. Path. **14**:637 (Nov.) 1932.

Twice coming under Milian's influence, he was twice compelled to renounce Milian's methods because of fatal results. Sicard [95] reported the case of a patient with paresis in whom icterus developed during treatment. Further specific therapy, though ordered to be stopped, was by accident continued; the result was death of acute yellow atrophy. Chargin and Orgel [102] caused frank jaundice to appear by continuing to treat three patients in whom during arsphenamine therapy latent icterus had already developed, according to the estimation of the bilirubin content of the blood. Schneider,[119] Gerrard [92] and Dixon, Campbell and Hanna [120] had similar experiences. Todd [121] also expressed the opinion that jaundice is aggravated by the continuation of treatment with arsphenamine. Nicaud[122] reported three cases in which the condition either grew worse or recurred after therapy was resumed, one patient suffering four relapses. Leredde and Kuenemann [123] reported a case in which jaundice recurred six times before treatment with arsphenamine was finally abandoned. Laurent,[89] Stümpke [124] and Wechselmann and Hohorst [125] had similar experiences. One of my patients had two attacks of paratherapeutic icterus ten years apart. These reports gain greater significance from the consideration of the following facts: (1) I have not been able to find in the literature a record of a relapse with nonspecific therapy; (2) there were no deaths (save in case 1) or recurrences in the thirty-one cases I observed, although all the patients were treated with nonspecific therapy, with the addition of bismuth in a few instances.

9. Relation of Jaundice Following Arsphenamine Therapy to Epidemic or Endemic Catarrhal Jaundice.—It remains now to consider the problem of the identity of paratherapeutic icterus with epidemic or endemic catarrhal jaundice. No definite evidence of such an identity has yet been presented. However, Stokes, Reudemann and Lemon,[40] Ruge [42] and many others have expressed the opinion that the increase

119. Schneider, P.: Untersuchungen über den Bilirubingehalt bei Salvarsanquecksilber, Dermat. Wchnschr. **74**:228 and 250, 1922.

120. Dixon, H. A.; Campbell, W. R., and Hanna, M. I.: Control of Arsphenamine Treatment by Liver Function Tests, Canad. M. A. J. **16**:551 (May) 1926.

121. Todd, A. T.: Post-Salvarsan Jaundice, Lancet **1**:632 (March 26) 1921.

122. Nicaud, P.: Jaundice Following Treatment with Salvarsan and Neosalvarsan, Presse méd. **28**:322, 1920.

123. Leredde and Kuenemann: Les accidents de 606 et leurs causes: Statistique de 416 injections intraveineuses, Bull. Soc. franç. de dermat. et syph. **22**:449, 1911.

124. Stümpke, G.: Zur Frage des Ikterus nach Salvarsan, Med. Klin. **18**:295, 1922.

125. Wechselmann, W., and Hohorst, W.: Ueber den Einfluss der Salvarsanbehandlung auf den Bilirubingehalt des Blutserums, Arch. f. Dermat. u. Syph. **136**:285, 1921.

in the occurrence of paratherapeutic icterus is explained by a simultaneous increase in the occurrence of catarrhal jaundice. Epidemics of catarrhal jaundice are common, and they occurred with frequency before the era of arsphenamine therapy. Hennig [126] in 1890 reported eighty-six epidemics of jaundice in all quarters of the world during the preceding one hundred and ninety years; yet in none of these epidemics was an unusual proportion of syphilitic persons noted. However, if paratherapeutic icterus today is to be regarded as catarrhal jaundice, the proportion of syphilitic persons in the latter group would be astounding (approximately 20 per cent, according to my statistics).

Ruge, for instance, reported statistics on a large number of cases of jaundice in the German marine, which showed that the proportion of persons treated for syphilis who suffered from jaundice was approximately eight times greater than the general incidence of jaundice in the entire group. Todd [121] in 1921 reported statistics on the incidence of jaundice among the British troops on the Rhine, where catarrhal jaundice was endemic at the time. Of syphilitic soldiers treated with the arsphenamines, jaundice developed in 8.3 per cent, while only 0.3 per cent of the rest of the troops were affected.

Statistics at the Mount Sinai Hospital indicate that during the past five years the incidence of paratherapeutic jaundice among syphilitic persons was four times greater than the incidence of catarrhal jaundice and acute yellow atrophy among the patients on the general medical list.

Furthermore, as was pointed out before, the curve of incidence of cases of late icterus rules out the possibility of a chance intercurrent disease being responsible for the jaundice. Moreover, Zimmern [127] and Ruge [42] pointed out that during the World War the incidence of catarrhal jaundice in Germany did not increase remarkably, while the incidence of jaundice associated with arsphenamine therapy decidedly did. The graphic data of Müller [128] also show that catarrhal and arsphenamine jaundice did not predominate during the same periods.

There are other circumstances leading to the conclusion that catarrhal jaundice is not identical with paratherapeutic icterus. For instance, the severity of the jaundice, as measured by the proportion of cases of acute yellow atrophy, is generally greater in cases of paratherapeutic icterus than in cases of catarrhal jaundice, as demonstrated by the statistics of both Heinrichsdorff [70] and Ruge.[42] The series of

126. Hennig, A.: Ueber epidemischen Icterus, Samml. klin. Vortr. no. 8, 1890 (Inn. Med. no. 4, p. 77).

127. Zimmern, F.: Spätikterus nach Salvarsan, Dermat. Ztschr. **27**:138, 1919.

128. Müller, I.: Zur Statistik der Lebererkrankungen im Zeitraum von Jan. 1914 bis März 1922, Klin. Wchnschr. **1**:835, 1922.

cases mentioned in the reports of the Medical Research Council [129] of Great Britain and the series reported by Silbergleit and Föckler [130] were attended by extremely high mortality. Kuznitzky and Fuchs [131] also expressed the opinion that the increase in the incidence of acute yellow atrophy following arsphenamine therapy was absolute and was not related to an increase in the incidence of catarrhal jaundice in recent years.

All these observations speak for the fundamental independence of paratherapeutic icterus and of catarrhal jaundice, although I shall later point out that the conditions may sometimes act together in summation or potentiation.

10. Factors Which Predispose to the Occurrence of Arsphenamine Jaundice: Endemic Catarrhal Jaundice, Malnutrition, Etc.—From the foregoing facts it is concluded that paratherapeutic icterus is caused fundamentally by the effect of the arsphenamines on the liver. The word fundamentally is emphasized because there are apparently other contributory or predisposing factors of definite, though less, importance, which may act with the arsphenamines as summating or potentiating agents.

Masson [132] demonstrated experimentally that if the liver of an animal is damaged by chloroform, the proportion of a subsequent dose of arsphenamine taken up by this injured liver will be greater than that taken up by the normal liver; Rössle [112] reported similar results. Thiroux and his associates [133] found that if sheep serum, which is extremely toxic to rabbits when injected intravenously, is injected subcutaneously no harmful effect is apparent. But, if this is followed by a dose of arsphenamine, jaundice and hepatic damage ensue. Control animals given horse serum and arsphenamine were unaffected. These experiments suggest that another hepatotoxic agent acting on the liver simultaneously with the arsphenamine may potentiate the effect of the latter.

129. Reports of the Salvarsan Committee, Toxic Effect Following the Employment of Arsenobenzol Preparations, Medical Research Council, Special Report Series, no. 66, London, His Majesty's Stationery Office, 1922; Result of the Examination of the Tissues from Eight Cases of Death Following Injection of Salvarsan, Medical Research Council, Special Report Series, no. 55, London, His Majesty's Stationery Office, 1920.

130. Silbergleit, H., and Föckler: On Icterus and Acute Yellow Atrophy in Syphilitic Patients in Relation to Neosalvarsan Treatment, Ztschr. f. klin. Med. **88**:333, 1919.

131. Kuznitzky, E., and Fuchs: Ueber Nebenwirkungen verschiedener Salvarsanpräparate besonders in Frauen, Arch. f. Dermat. u. Syph. **138**:222, 1922.

132. Masson, L. V.: Pathogénie clinique et expérimentale des ictères dits arsénobenzoliques, Thèse de Strasbourg, 1925.

133. Thiroux, A.; Bouvelet, C., and Arlo, J.: Hypertoxicité du novarsénobenzol pour les lapins préparés par injections souscoutanées de sérum de moutons, Compt. rend. Soc. de biol. **88**:491, 1923.

At the British military hospital at Cherryhinton an "epidemic" of thirty-seven cases of arsphenamine jaundice occurred, with a mortality of 50 per cent from acute yellow atrophy, although there were no cases of jaundice in the hospital among a large number of patients with gonorrhea. There was a small epidemic of catarrhal jaundice in the same neighborhood at the same time, which chiefly affected school children.[129] With the observations on this "epidemic," those of Todd and Ruge mentioned in the preceding section should be considered.

Stokes, Reudemann and Lemon,[40] of the Mayo Clinic, reported that from 1916 to 1918 they observed only six cases of paratherapeutic icterus; among a similar total number of patients treated with essentially the same technic, type and dose of drug from 1918 to 1920, there were sixty-four cases. They pointed out that during the latter two years there was a series of small epidemics of catarrhal jaundice in the region of Rochester, Minn. In addition, in most of the cases paratherapeutic icterus followed closely an infection of the upper respiratory tract. Nast also stressed the rôle of infections of the upper respiratory tract in predisposing to paratherapeutic icterus. Stokes and his associates mentioned arthritis as a possible factor predisposing to arsphenamine jaundice. One of Severin and Heinrichsdorff's patients and several of our patients complained of arthritis or arthritic pains shortly before the onset of the jaundice.

It seems logical that when two hepatotoxic agents, each in itself insufficient to cause jaundice, affect a particular person they may together bring about the appearance of jaundice. In an epidemic of catarrhal jaundice there must be many latent cases in which the administration of arsphenamine might precipitate frank jaundice. The contributory factor may also be any infection of the respiratory tract or intestinal, arthritic or general infection or toxin that is distinguished by a hepatotropic toxic effect. Renal diseases may also aggravate the susceptibility to hepatic degeneration. Voegtlin [76] noted an increase in the toxicity of arsphenamine to the liver after ligation of the ureters, and Lazerat [134] and Nicaud [122] suggested that functional renal damage may retard the excretion of arsenic and so overload the liver.

Other factors which have been considered as exercising a deleterious effect on the liver and thus predisposing to jaundice are general debility, malnutrition, starvation and perhaps even certain vitamin deficiencies, pregnancy and the puerperium. Kraus,[135] Wolf,[16] Hoppe-Seyler [136]

134. Lazerat, J.: Contribution à l'étude de l'ictère grave apparaissant chez les syphilitiques traités par les arséno-benzènes, Thèse de Paris, 1926.

135. Kraus, F.: Ueber Ikterus als "führendes" Symptom, Berl. klin. Wchnschr. **58**:725, 1921.

136. Hoppe-Seyler, G.: Ueber Lebererkrankungen und ihre Behandlung unter dem Einfluss der Kriegsverhältnisse, Med. Klin. **15**:1105, 1919.

and Gutmann [61] emphasized these factors. It was pointed out that in Holland and Switzerland, where the nutritional effects of the World War were felt least, jaundice was comparatively rare. On the other hand, other observers stated that jaundice was most prevalent after 1918, when nutrition was considerably improved; but one cannot be certain that the effects of years of privation can be remedied in a short time. A number of my cases of paratherapeutic icterus occurred among the Latin-American inhabitants of New York, whose unhygienic environment and improper nutrition are well known.

SUMMARY

An investigation has been made of the circumstances associated with the occurrence of jaundice complicating arsphenamine therapy. It was first pointed out that benign and fatal (acute yellow atrophy) jaundice must be considered as the same disease, differing only in severity. Definite anatomic syphilis of the liver (gumma, etc.) is not associated with frank jaundice or with the syndrome of catarrhal jaundice or of acute yellow atrophy.

Before the introduction of arsphenamine frank jaundice in persons with syphilis was rare (an incidence of 0.37 per cent) and occurred only in the secondary stage. This former rarity of jaundice with syphilis was compared with its subsequent frequency in both secondary syphilis and tertiary syphilis following treatment with the arsphenamines. This frequency of incidence is so striking as to permit the conclusion that paratherapeutic icterus is caused by the direct toxic effect of the arsphenamines on the liver.

In favor of this view the following facts were pointed out: 1. Experimentally, arsphenamine damages the liver and its functions, and it is possible to cause jaundice in dogs by giving large doses of the arsphenamines. 2. The incidence of paratherapeutic jaundice increases roughly with the quantity of drug used. 3. Paratherapeutic jaundice is also observed as a complication in cases of nonsyphilitic diseases in which treatment is carried out by means of the arsphenamines. 4. There is an occasional concomitant occurrence of other types of intoxications caused by arsphenamine, such as arsphenamine dermatitis.

Against the theory that paratherapeutic icterus is caused by active syphilis of the liver or represents a Herxheimer reaction are the following observations: 1. The patient is usually receiving active treatment with a specific drug. 2. The Wassermann reaction is often negative. 3. No other concomitant lesions of active syphilis are found. 4. In fatal cases S. pallida is not found in the liver.

While in cases of jaundice with true recurrent secondary syphilis the Wassermann reaction is always positive, an exanthema is present and there is a history of insufficient treatment, these phenomena are absent in cases of late icterus, which is therefore not to be regarded as an active syphilitic hepatorecurrence. The objection that the delay between the last injection of arsphenamine and the first appearance of jaundice in cases of late icterus speaks against the arsphenamine etiology of paratherapeutic icterus was met by the following facts: 1. The period of latency is not a haphazard interval but is limited to approximately ten months. 2. Even in the absence of jaundice, the liver and its functions may be damaged during this latent period. 3. Other well known hepatotoxins often show a similar latent period.

It has been demonstrated experimentally that young and regenerating hepatic tissue is relatively insusceptible to hepatotoxins. A liver injured by a certain hepatotoxin and therefore undergoing regeneration can subsequently withstand larger doses of the same toxic substance. Therefore, when arsphenamine is given to a patient suffering from paratherapeutic icterus, it is usually received by a liver which contains regenerating or recently regenerated tissue and which therefore is less susceptible to injury than the original tissue. This fact probably explains the paradoxical cure of arsphenamine jaundice during continued arsphenamine therapy. Attention was also called to the fact that in a small proportion of cases resumption of treatment with arsphenamine causes an aggravation of the jaundice or death from acute yellow atrophy of the liver and that in some cases if treatment with arsphenamine is resumed after the jaundice has disappeared a relapse may take place.

Paratherapeutic icterus cannot be considered identical with epidemic or endemic catarrhal jaundice; it is distinguishable by epidemiological and other evidence.

Finally, attention was drawn to the possibility that certain infections, toxins and other debilitating factors may act on the liver in such manner as to summate with, or potentiate, the effect of the arsphenamine.

CONCLUSIONS

Jaundice of the type seen in catarrhal icterus does not occur with definite anatomic syphilis of the liver.

Jaundice occurs in 0.37 per cent of untreated persons with secondary syphilis and is caused by the toxic effect of the generalized spirochetosis.

Since the introduction of arsphenamine, jaundice has been observed with tremendously increased frequency, and it has been noted both in cases of secondary syphilis and in cases of tertiary syphilis.

The arsphenamines are hepatotoxic and are responsible for the syndrome of paratherapeutic icterus. The latent period of late icterus does not militate against this concept.

The apparent greater tolerance for the arsphenamines displayed by syphilitic persons suffering from paratherapeutic icterus is attributed to the greater resistance to hepatic poisons of recently regenerated hepatic tissue.

Paratherapeutic icterus is not identical etiologically with catarrhal jaundice.

The significance of predisposing and contributory factors, such as endemic catarrhal jaundice, malnutrition, etc., has been discussed.

ANALYSIS OF CASES

The table contains an analysis of the cases observed in the medical service of the Mount Sinai Hospital during the past five years. The number of cases of tertiary syphilis of the liver and the combined total number of cases of catarrhal jaundice, acute and subacute yellow atrophy and coarse nodular cirrhosis have been included for comparison.

In the cases of late icterus the average length of the period elapsed since the last injection of arsphenamine was almost four months, an average delay much longer than that usually reported in the literature. The shortest interval was two weeks, and the longest eight months.

CASE 1. *History and Course.*—V. L., a retired fruit broker, aged 65, was admitted to the service of Dr. B. S. Oppenheimer on Nov. 6, 1933. His wife had had several miscarriages; however, the patient said that he had not had venereal disease. He was known to have had hypertension for ten years and had been suffering from dyspnea on exertion for the past five years.

Recently, during the course of a routine physical examination the Wassermann reaction of the blood was found to be positive. The patient then received a course of intravenous arsenical antisyphilitic injections, the last injection of which was given two weeks before he was admitted to the hospital. Shortly after the last injection he experienced a chill. Four days after the chill his right wrist became red, hot, swollen and painful, and four days later he vomited several times and became jaundiced.

Physical examination revealed the patient to be decrepit and jaundiced. His pupils reacted normally. The lungs were clear. The heart was enlarged downward and to the left, and there were a systolic and a diastolic murmur at the base. The blood pressure was 185 systolic and 85 diastolic. The right wrist and the right ankle were swollen, red and tender. The neurologic examination gave negative results. The diagnosis was paratherapeutic icterus, syphilitic aortitis and gonorrheal arthritis.

The temperature varied between 101 and 103 F. The white blood cell count was 28,600 per cubic millimeter, 92 per cent of the cells being polymorphonuclears. The van den Bergh reaction in the direct phase was prompt and positive and in the indirect phase showed 2.5 mg. of bilirubin per hundred cubic centimeters of serum. The icteric index was 35. The total phase showed that the cholesterol content of the blood was 160 mg. per hundred cubic centimeters, and the esterified

fraction was 65 mg. The Wassermann and Kahn reactions of the blood were 4 plus. The urine contained tyrosine and urobilin. The stool was brown at all times. Fluid obtained on aspiration of the right wrist joint revealed gram-negative intracellular diplococci, which proved on culture to be meningococci. The patient was given a diet high in carbohydrates. Specific treatment was not given.

Three days after the patient was admitted he became stuporous. His neck was rigid, and the Kernig sign was elicited. A spinal tap yielded cloudy fluid, containing 2,000 cells per cubic millimeter, of which 70 per cent were polymorphonuclear leukocytes. Meningococci were present in the culture of the fluid. Antimeningococcic serum was administered intraspinally, intramuscularly and intravenously. The patient soon brightened mentally, the fever and swollen joints subsided, the spinal fluid became sterile and the cell count diminished rapidly.

The Incidence of Jaundice With Syphilis

Condition		Total Number of Cases	Deaths
Icterus syphiliticus praecox		4	0
Paratherapeutic icterus with syphilis		24	1 (case 1)
Secondary syphilis	4		
Tertiary syphilis	20		
Total	24		
Early icterus	12		
Late icterus	12		
Total	24		
Paratherapeutic icterus in nonsyphilitic persons		3	0
Early icterus	2		
Late icterus	1		
Total	3		
Total number of cases of jaundice with either syphilis or arsphenamine therapy or both		31	1
Tertiary syphilis of the liver without jaundice (one patient faintly jaundiced)		12	6
Catarrhal jaundice, acute and subacute yellow atrophy and coarse nodular cirrhosis in nonsyphilitic persons		99	14

The patient had been doing well for two weeks and was out of bed when he relapsed into stupor. The spinal fluid at this time was normal. The icteric index was down to 15, and the van den Bergh test in the direct phase gave negative results and in the indirect phase showed 0.2 mg. of bilirubin per hundred cubic centimeters. The urine no longer contained tyrosine but still showed urobilin. The cholesterol content of the blood had diminished to 115 mg. per hundred cubic centimeters, with only traces of cholesterol esters. The scleras were still slightly jaundiced.

The patient remained in a stupor and died four days after his relapse. The cause of death was clinically unclear.

Postmortem Examination.—This was carried out on December 6 by Dr. Lichtenstein, Dr. Jarcho and Dr. Bender. The anatomic diagnosis was confluent bronchopneumonia of the lower lobe of the left lung (the cause of death), chronic and acute bronchitis, healing meningococcic meningitis, meningococcic arthritis of the right wrist and right ankle, focal parenchymatous necrosis of the liver, with

atrophy, fibrosis and regeneration, icterus (slight), syphilitic mesaortitis, chronic rheumatic valvulitis of the mitral, aortic and tricuspid valves and acute infectious splenic swelling.

Examination of the Liver: The liver was distinctly smaller than normal; it weighed 1,000 Gm. Its capsule was finely and diffusely wrinkled. The consistency was flabby throughout, the left lobe seeming flabbier and more atrophic than the right lobe. The cut surface was yellowish brown. The normal lobulation was distinctly visible, but the individual lobules were small. The hepatic and portal vessels were grossly normal. The extrahepatic bile ducts and the gallbladder appeared to be normal. The gallbladder contained dark green, viscid bile.

Sections of the liver were stained with hematoxylin and eosin, Van Gieson's stain and sudan III and by the silver impregnation method. The normal lobular

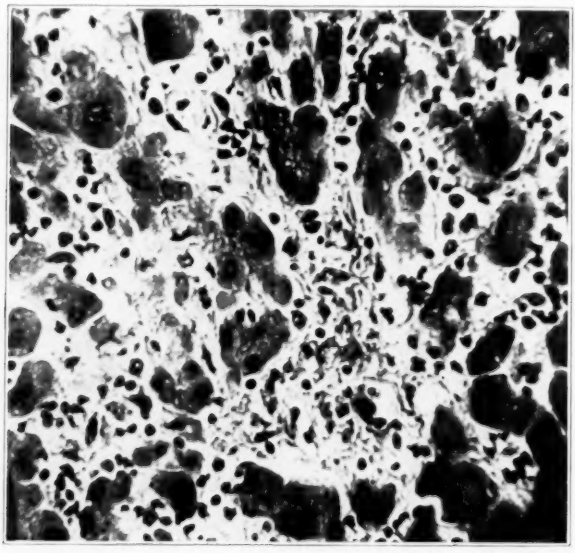


Fig. 1.—Foci of degeneration of hepatic cells, with an invasion of lymphocytes and polymorphonuclear leukocytes. Hematoxylin and eosin stain.

structure of the liver and the normal appearance of the cords of the liver cells were generally easily recognizable on low power examination in sections made of the right lobe of the liver. In sections of the left lobe the cords were broken up by a dissociation of each cell from its neighbors. Scattered about the liver lobule, but more commonly located in the central zone, were foci varying in size from that of a single cell to one fifth of a lobule, in which the hepatic architecture was not present or was discernible with difficulty. The liver cells were polygonal, with mottled granular cytoplasm and round vesicular nuclei with a single large reddish-blue nucleolus. A moderate degree of fatty vacuolation of the cells in the central areas was noted. Here and there, singly or in groups, as mentioned previously, cells were seen the cytoplasm of which was very granular, stained faintly with eosin and contained much granular green bile pigment. Many of

these cells were shrunken and rounded, sometimes with only an amorphous mass of débris remaining. The nuclei of these cells were faint or absent. In such areas the capillaries were wide and the framework was conspicuous. A few bile thrombi were noted in the bile canaliculi. Occasionally an area of such cells was invaded by lymphocytes and a few polymorphonuclear leukocytes (fig. 1). Elsewhere these foci contained a few thickened collagen fibers which stained red with the Van Gieson stain or were entirely replaced by small scars (fig. 2). The reticular framework throughout, as revealed by the Van Gieson and the silver stain, was coarse and thickened. In the vicinity of foci of degeneration large cells with copious amounts of cytoplasm containing little or no bile pigment were seen. Their nuclei were large, dark-staining and somewhat irregular and often contained

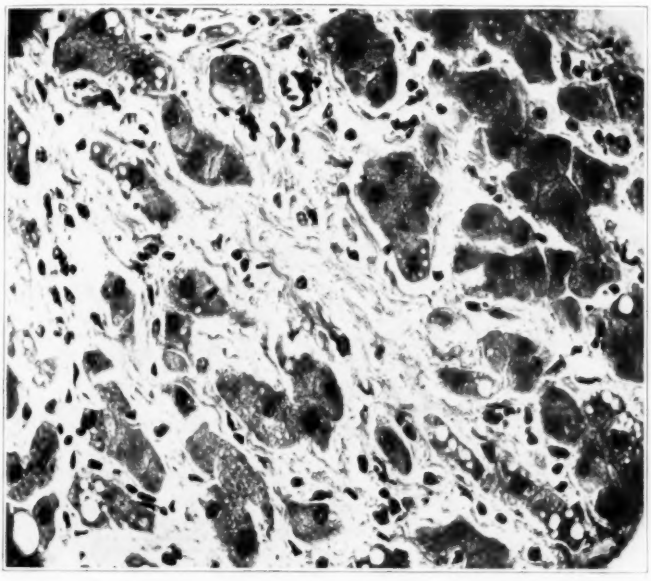


Fig. 2.—A collagenous scar in the parenchyma of the liver. Hematoxylin and eosin stain.

multiple nucleoli. Cells with multiple nuclei were common, but no mitoses were discovered. A few nuclei contained a large clear vacuole, which pressed the chromatin to the periphery—so-called glycogen degeneration of the nucleus. The Kupffer cells were generally spindle-shaped and sometimes showed small cytoplasmic vacuoles. Some round cells were present in the sinusoids, which in the central zones were moderately congested with red blood cells. Many of the portal spaces were heavily infiltrated with lymphocytes and polymorphonuclear leukocytes, and in some instances the spaces showed proliferation of fibroblasts and thickening of the connective tissue. The portal vessels and bile ducts were without significant change.

This case appears to have been one of paratherapeutic icterus in which the meningococcic infection was possibly a factor contributing to a slight extent toward the degeneration of the liver. However, since jaundice is unknown in cases of meningococcic infection, there can be little doubt that the injections of arsphenamine were of primary importance. Death occurred from confluent bronchopneumonia at a time when the jaundice had almost entirely disappeared and the liver was evidently improving. The opportunity to examine the liver at this stage was very fortunate, since it demonstrated clearly both the focal necrosis of the liver and the processes of healing, i. e., regeneration and scarring. There were no indications of an acute or chronic inflammatory process in the liver.

CASE 2.—I. L. was a Pole aged 42. His past history was irrelevant. Eight years previously the patient had a chancre. The Wassermann reaction was 4 plus, and treatment was begun with arsphenamine and mercury. The injections of arsphenamine were frequently followed by seizures of mental confusion. Four years later treatment was resumed, with similar reactions. One year before hospitalization the Wassermann reaction was 2 plus, and treatment with neoarsphenamine was started. The reaction was so severe that intravenous therapy had to be abandoned after several injections, and treatment was continued with bismuth.

Seven and a half months after the last intravenous injection the patient complained of weakness and anorexia, and three days later he became frankly jaundiced. He was well nourished and in good general condition. The liver was tender and sharp-edged and was felt 3 cm. beneath the costal margin; the spleen was not palpable. The chest was normal. There was evidence of mild dementia paralytica. The Wassermann reaction was negative, and the Kahn reaction was reported as plus-minus. The hemoglobin content was 98 per cent and the white blood cell count was 6,900 per cubic millimeter, with polymorphonuclear leukocytes, 76 per cent, lymphocytes, 14 per cent, monocytes, 4 per cent and eosinophils, 6 per cent. The stool was always brown and gave a positive reaction for urobilin, as did the urine, which was deeply stained with bile. The urea and sugar contents of the blood were normal. The cholesterol content was: total, 250 mg. per hundred cubic centimeters, and the esterified fraction, 125 mg., or 50 per cent of the total (normal). The icteric index was 60; the van den Bergh reaction in the direct phase was delayed and positive and in the indirect phase showed a proportion of 1:20,000, or 5 mg. of bilirubin per hundred cubic centimeters of blood serum. Because of the nonobstructive jaundice and the history of intolerance for arsphenamine, a tentative diagnosis of paratherapeutic icterus was made, and conservative treatment was instituted. However, anorexia and nausea prevented the use of an adequate diet, there was mild fever, the liver became further enlarged and ascites appeared; paracentesis yielded 300 cc. of bile-stained fluid. The icteric index rose to 135, and the van den Bergh reaction in the direct phase was prompt and positive and in the indirect phase showed a proportion of 1:10,000, or 10 mg. of bilirubin. The total cholesterol content was 260 mg., and the esterified fraction, 55 mg., or 20 per cent of the total—an indication of parenchymatous hepatic damage. The patient looked, in general, much worse. An attempt to combat anorexia and nausea with small injections of insulin met with success. Potassium iodide was given by mouth, and a suspension of bismuth subsalicylate in oil was administered intramuscularly. Improvement was gradual but satisfactory. In forty-three days

the patient was discharged; the icterus index was then 21. When examined in the follow-up clinic several months later, the patient was well except for signs of mild dementia paralytica.

One may here remark on the long history of intolerance to arsphenamine, the disappearance of anorexia and nausea following insulin therapy and the suspicion that a specific antisyphilitic effect of the bismuth may have been responsible for the improvement. However, in regard to the latter, it must not be forgotten that this patient had ascites and that bismuth is a diuretic.

CASE 3.—C. C., a Puerto Rican woman aged 35, ten years previously had an attack of painless jaundice following intravenous antisyphilitic treatment and recovered. Some time after this attack additional treatment was given without complication. During a recent pregnancy she received injections of arsphenamine until delivery; after this she complained of fatigue and frequently of nausea and vomiting. Four months post partum she noted that she was jaundiced, and four months later she was admitted to the hospital, distinctly undernourished, toxic and deeply icteric. The chest was normal. The liver was enlarged, firm and grossly irregular with a large lappet extending downward almost into the right iliac fossa. The spleen was large and firm. The Wassermann reaction was 3 plus; the Kahn reaction was 3 plus; the hemoglobin content was 35 per cent, and the white blood cell count was 3,000 per cubic millimeter, with polymorphonuclear leukocytes 64 per cent, lymphocytes 33 per cent and eosinophils 3 per cent. The stool was light brown; both the stool and the urine were deeply colored with bile. The icterus index was 135; the van den Bergh reaction in the direct phase was prompt and positive and in the indirect phase showed a proportion of 1 to 40,000, or 2.5 mg. of bilirubin. The cholesterol content was 135 mg. per hundred cubic centimeters, and the esterified fraction was 25 mg., or 19 per cent of the total. The sugar and urea content of the blood were normal. Because of the long continued jaundice and the irregular function of the liver the diagnosis was coarse nodular cirrhosis caused by delayed arsphenamine poisoning and favored by the puerperium, anemia and malnutrition. Impending cholemia was feared. Because of vomiting it was impossible to establish the usual regimen. An intravenous drip of a 10 per cent solution of dextrose in distilled water, with sufficient insulin to prevent glycosuria, was therefore begun. Though this patient appeared to be sicker than the one in case 2, bismuth was withheld for reasons of control. Improvement was slow and gradual. The intravenous injection of dextrose was discontinued as soon as peroral feeding could be tolerated. The patient eventually left the hospital free from symptoms, although the liver was still nodular.

This case suggests that the salutary effect, if any, of bismuth in case 2 was mediated not by its specific antisyphilitic power but by its effect on the disordered water metabolism. The suspicion that the strain of pregnancy, anemia and malnutrition were contributory etiologic factors abetting the arsphenamine is very strong.

CASE 4.—R. A., a man aged 30, was a painter. Following a dietary indiscretion abdominal pain developed, and the patient vomited frequently. He had high fever and became jaundiced the day before he was admitted to the hospital. He appeared to be severely toxic, dehydrated and worn. The liver was small on percussion and

could not be palpated. The icterus index and the values for the van den Bergh reaction were elevated, and the urea content of the blood rose as high as 120 mg. per hundred cubic centimeters. The concentration of urine was high. With general treatment and forcing of fluids, the jaundice disappeared rapidly; the azotemia disppeared a little less quickly. The blood pressure was not elevated; there was no evidence of lead poisoning.

The patient stated that he had had a chancre eleven years previously, which had been adequately treated. The Wassermann test had become negative, and it continued to be so.

This was the only case observed in which by any stretch of imagination the condition might be suspected of being tertiary syphilis and jaundice without recent treatment with arsphenamine. However, since the syphilis had been adequately treated years before, the patient could not be regarded as having active syphilis. The case is rather obviously one of intoxication—gastro-intestinal, hepatic and renal—not related to syphilis. Examination for Spirochaeta icterohaemorrhagiae was not performed.

INFANTILISM AND DIABETES MELLITUS

A REPORT OF EIGHT CASES

R. B. GIBSON, PH.D.
AND
W. M. FOWLER, M.D.
IOWA CITY

A group of young patients with the manifestations of diabetes mellitus, sexual infantilism and varying degrees of dwarfism has been observed. These patients not only present a definite syndrome but are of interest in view of the recent advances which have been made in the knowledge of the anterior lobe of the pituitary gland. They demonstrate the occurrence of diabetes mellitus in association with hypofunction of the anterior lobe of the hypophysis in spite of the improbability of such a combination as indicated by experimentation with animals. As the result of pituitary dysfunction, as evidenced by dwarfism or at least by delayed adolescence, diabetic symptoms if present should be mild. In all eight cases the condition has been severe.

The functions of the anterior lobe of the pituitary gland have been summarized by Evans,[1] who ascribed to it growth, gonadotropic, lactogenic, thyrotropic and adrenotropic hormones; in addition to a factor regulating fat metabolism and a diabetogenic hormone controlling carbohydrate metabolism. The relationship between carbohydrate metabolism and the anterior lobe of the pituitary gland has been frequently emphasized. Acromegaly, especially in the early or active stage, is associated with glycosuria and hyperglycemia in from 10 to 40 per cent of the cases.[2] On the other hand, cases of hypophyseal dwarfism have been reported in which there were lowered dextrose tolerance and an increased sensitivity to insulin.[3] The experimental evidence in regard to this relationship was summarized and augmented

From the Pathological Chemistry Laboratory and the Department of Internal Medicine, University Hospitals, the State University of Iowa.

1. Evans, H. M.: Present Position of Our Knowledge of Anterior Pituitary Function, J. A. M. A. **101**:425 (Aug. 5) 1933. Collip, J. B.: Diabetogenic, Thyrotropic, Adrenotropic and Parathyrotropic Factors of Pituitary, ibid. **104**:827 (March 9) 1935; 916 (March 16) 1935.

2. John, H. J.: The Possible Relationship Between Acromegaly and Diabetes, Arch. Int. Med. **37**:489 (April) 1926.

3. Lucke, H.: Der Kohlehydratstoffwechsel bei Erkrankungen des Hypophysenvorderlappens, Ztschr. f. klin. Med. **122**:23, 1932.

by Barnes and Regan,[4] who showed that hypophysectomy in dogs produces an increased sensitivity to insulin and leads to convulsions due to hypoglycemia during a period of fasting. In dogs in which hypophysectomy and pancreatectomy have been performed the blood sugar level remains approximately normal, and diabetes does not develop as it does in dogs subjected to removal of the pancreas alone. The dextrose tolerance in these animals is somewhat reduced, although large amounts of dextrose can be given by mouth without the appearance of glycosuria. Glycosuria can be produced at will in these dogs, however, by the administration of an extract of the anterior lobe of the pituitary gland, and in five of six normal dogs glycosuria and a decreased sugar tolerance were produced by the same means.

It is well recognized that certain diseases, infections and metabolic disturbances in childhood may prevent normal growth and development and that these conditions must be excluded before a diagnosis of hypophyseal infantilism is made. In the group of cases reported here the diabetes mellitus had either not appeared or was adequately controlled at the age of puberty, and it seems doubtful whether this was the cause of the maldevelopment. Infantilism was manifested in the girls by amenorrhea and complete or partial failure of development of the secondary sex characteristics. The breasts were small and undeveloped; the external genitalia and the uterus were infantile in type, and there was an absence or a very sparse growth of pubic and axillary hair. In the boys the same absence or sparse growth of hair was noted, as well as the infantile type of genitalia. A certain degree of dwarfism was present in all. The physical characteristics consisted of a small but well proportioned skeletal and muscular system, and an absence of or a very slight tendency to obesity, in addition to the sexual infantilism. The mentality was normal; manifestations described are those commonly interpreted as being due to a deficiency of the gonadotropic and growth hormones of the anterior lobe of the pituitary gland.[5] They correspond to the infantile proportionate type of dwarfism[6] in which there is no family history of a similar condition and in which none of the more common etiologic factors of dwarfism, such as achondroplasia, rickets or cretinism, is present. There was no evidence of malnutrition, and in all but two patients the diabetes had been fairly well controlled by an adequate diet for some years; in the two patients

4. Barnes, B. O., and Regan, J. F.: The Relation of the Anterior Pituitary to Carbohydrate Metabolism, Endocrinology **17**:522 (Sept.-Oct.) 1932.

5. Shelton, E. K.; Cavanaugh, L. A., and Evans, H. M.: Hypophyseal Infantilism: Treatment with Anterior Hypophyseal Extract, Am. J. Dis. Child. **47**:719 (April) 1934.

6. Barker, L. F.: A Case of Hypophyseal Dwarfism, Endocrinology **17**:647 (Nov.-Dec.) 1933.

mentioned the diabetes had developed only recently. A somewhat similar case was reported by Joslin.[7] John[8] reported cases of hypopituitarism in five patients; one of these had diabetes; one had a mild case of diabetes, and three had prediabetic symptoms, but all were obese, and the cases were not comparable to those reported here. Steel[9] reported a case of diabetes mellitus in association with dystrophia adiposa genitalis and diabetes insipidus. Cases similar to those observed by us were reported by Apert[10] and by Gardiner-Hill,[11] both of whom expressed the belief that the infantilism was secondary to the diabetes and reported improvement in growth and sexual development following management of diabetes. Fliederbaum[12] also reported two cases and expressed the belief that they were of insulogenic origin. He further stated that insulin is indicated in the treatment of certain cases of infantilism without diabetes.

REPORT OF CASES

CASE 1.—D. M., a white girl aged 17 years, was admitted to the University Hospitals on Aug. 1, 1933, for management of diabetes. There was a rather indefinite history of polyphagia and polydipsia dating back to 1929. In 1931 the patient began to feel weak and tired, and in March 1932 she consulted a physician, who advised a high caloric diet, on which she gained 8 pounds (3.6 Kg.). There was no glycosuria at that time. Early in the spring of 1933 the patient again began to feel weak and tired and to lose weight. At that time sugar was found in the urine by her physician, and she was placed on a regimen of diet and insulin. There was no family history of diabetes, and all the other members of her family had developed normally.

The patient was well proportioned but poorly nourished and appeared to be about 12 years of age. She was 5 feet, 1 inch (about 154.5 cm.) tall and weighed 80 pounds (about 36.4 Kg.). She had never menstruated. The axillary hair was normal, but the pubic hair was sparse. The breasts and nipples were undeveloped and were of infantile type, and the external genitalia were small and infantile. Otherwise physical examination gave negative results, except that congenital bilateral cataracts were noted.

The Wassermann reaction was negative. The hemoglobin content of the blood was 95 per cent of normal, and the erythrocyte count was 5,110,000. The urine

7. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 877 [case 3620].

8. John, H. J.: Hypopituitarism and Diabetes, Endocrinology **9**:397 (Sept.-Oct.) 1925.

9. Steel, R. S.: Diabetes and Dyspituitarism, Proc. Staff Meet., Mayo Clin. **2**:216 (Sept. 14) 1927.

10. Apert, E.: Insulin in Diabetes with Infantilism, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:894 (June 20) 1924.

11. Gardiner-Hill, H.: Dwarfism and Infantilism, Practitioner **125**:97 (July) 1930.

12. Fliederbaum, J.: Infantilismus insulogenes, Ztschr. f. klin. Med. **24**:86, 1933.

was normal except for the presence of sugar. The basal metabolic rate was plus 19 per cent. Roentgenograms showed the sella turcica to be small, measuring 9 by 4 mm.

The blood sugar content on admission was 266 mg. per hundred cubic centimeters. The patient was given a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat, with insulin in doses of 22 and 15 units (before breakfast and before supper). The blood sugar content at 9 a. m. had dropped to 124 mg. She was discharged on Aug. 9, 1933, at which time she was receiving insulin in doses of 25 and 15 units (before breakfast and before supper), but some glycosuria persisted. She did not do well at home and was again admitted to the hospital on October 19. Her weight had fallen to 72½ pounds (about 33 Kg.). An injection of insulin was given at noon, as the blood sugar values in the afternoon were high, and her condition was controlled fairly well by insulin in doses of 18, 7 and 12 units each day. Injections of the anterior pituitary-like gonadotropic hormone from the urine of pregnant women decreased her carbohydrate tolerance slightly but had no other effect. She was discharged on November 24; the urine was free from sugar, and the last determination of the blood sugar content made before discharge showed 140 mg.

The management of the diabetes in the home was unsatisfactory, and she was admitted to the hospital again on Sept. 7, 1934. There were no further development of sex characteristics and no increase in stature. Control of the diabetes was difficult but was attained by insulin in doses of 3 units at 3 a. m., 7 units at 6:30 a. m., 4 units at noon and 12 units before supper. The urine was then free from sugar; no hypoglycemic reactions occurred and the blood sugar content two hours after meals was about 170 mg. She weighed 40 Kg. when she was discharged on October 22.

Case 2.—E. E., a white girl aged 20 years, came to the University Hospitals for the management of diabetes on June 1, 1933. She had suffered from boils and localized infections for three years but had noted polyuria and polydipsia for only the past year. Two weeks prior to admission diabetic acidosis and coma had developed, following which she took 30 units of insulin three times a day. There were no history of any serious illness and no family history of diabetes.

The patient began menstruating at the age of 16 years, but the cycles had been very irregular, with periods of amenorrhea lasting several months. The breasts were small and undeveloped. The uterus was infantile in type and congenitally retroverted. The cervix was small. The axillary and inguinal hair was of normal distribution. She was well proportioned but slender. Her height was 5 feet, 3 inches (160 cm.), and she weighed 93½ pounds (42.5 Kg.).

The Wassermann reaction was negative. The results of blood counts and determinations of the hemoglobin content were normal. The basal metabolic rate was plus 10 per cent. A roentgenogram of the sella turcica showed its size to be at the upper limit of normal, measuring 12 by 7 mm.

When she was admitted to the hospital the blood sugar content was 337 mg. per hundred cubic centimeters (at 2 p. m.), and there was glycosuria. The patient was given a diet of 60 Gm. of protein, 60 Gm. of carbohydrate and 150 Gm. of fat. She was desugarized on June 3 (the blood sugar content was 165 mg.); 17 units of insulin were given before breakfast and 10 units before supper. The blood sugar content was 142 mg. on June 6 but was increased with therapy with the anterior pituitary-like gonadotropic hormone from the urine of pregnant women to 167 mg. on June 9 and increased to 208 mg. on June 13. She was discharged on June 14. She was seen subsequently for the purpose of checking the diabetic

condition; her diet was increased, and the dosage of insulin readjusted. When she was examined on Jan. 4, 1934, her weight had increased to 121 pounds (about 55 Kg.), and she had been menstruating more frequently, although the flow was still scanty. On Jan. 7, 1935, the blood sugar content was 159 mg., but she had not menstruated for a year.

Case 3.—E. W., a white girl aged 16 years, was admitted to the University Hospitals for management of diabetes on May 6, 1933. Symptoms of diabetes had appeared three years before, and she had been given a diet and, later, insulin. She managed the diabetes for two years, then discontinued the insulin for financial reasons and after six months more ceased to follow the diet. There had been no previous illness of any consequence. One aunt and a cousin on the maternal side of the family had diabetes.

Although the axillary and pubic hair had appeared at the age of 14 years, the patient had never menstruated, and the secondary sex characteristics were poorly developed. The breasts were small and infantile in type; the pubic hair was scanty; the external genitalia were small, and on rectal examination the uterus was found to be small and anteverted, with the cervix conical in shape. The body was fairly well proportioned, although the hips were straight, the chest short and the abdomen rather long and somewhat obese. The patient was just under 5 feet (about 141 cm.) tall and weighed 105 pounds (about 47.7 Kg.). Her appearance was that of a girl from 12 to 14 years of age. The physical examination revealed that she was otherwise normal, and her mentality was above average.

The Wassermann reaction was negative. The percentage of hemoglobin and the blood counts were normal. The urine contained sugar on admission. The basal metabolic rate was plus 15 per cent. A roentgenogram of the skull showed a sella turcica of normal size, measuring 10 by 7 mm.

The blood sugar content was 362 mg. per hundred cubic centimeters on admission. The patient was given a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat. Thirty units of insulin before breakfast and 20 units before supper failed to control the glycosuria, and the patient was given insulin in divided doses (beginning May 10) and was desugarized with 10 units of insulin every three hours except at midnight. These doses were reduced progressively to 5 units, given every three hours except at midnight, and on June 27 (after seven weeks) the patient was again given two injections of insulin a day, 30 and 20 units. She was discharged on August 1, with no further improvement in dextrose tolerance; the urine was free from sugar and the last value for the blood sugar determined after a meal was 150 mg. Treatment with estrogenic substances (amniotin and theelin) had failed to induce menstruation. The patient weighed 111 pounds (about 50 Kg.) when she was discharged, having gained 6 pounds (2.8 Kg.).

Case 4.—E. B., a white girl aged 17 years, was admitted to the University Hospitals on March 9, 1933, because of diabetes mellitus and underdevelopment. Symptoms of diabetes had appeared when she was 8 years old, and she was placed on a diabetic diet at that time. After six months she was taken to a clinic, where insulin was prescribed in addition to the diet. She continued this regimen with no recurrence of the diabetic symptoms except occasional glycosuria, and her management in the home seems to have been excellent. The patient had been born at full term, weighing 6½ pounds (about 3,000 Gm.), and she had no serious illness in childhood. The members of her family were of normal size and none had diabetes.

The patient had developed normally until the age of 10 years, when she seemingly stopped growing. On admission she had the appearance of a child of

10 years except for a more mature facial expression. She was intelligent and was attending high school. The mammary glands and nipples were infantile, and the external genitalia were characteristic of prepubescence. There were no axillary or pubic hairs except a few on the labia majora. The labia minora were small, and the uterus was of the infantile type, with an elongated cervix. The patient had never menstruated. She was 4 feet, 8½ inches (143.5 cm.) tall and weighed 83½ pounds (about 38 Kg.). Physical examination showed that she was otherwise normal. She was normally proportioned.

Fig. 1.—E. B., aged 17 years. The height was 143.5 cm.; the weight, 38 Kg. The patient had been diabetic for nine years.

The Wassermann reaction was negative. The hemoglobin content of the blood was 92 per cent of normal, and there were 4,200,000 erythrocytes. The urine was normal except for sugar. Roentgenograms showed a normal sella turcica. There was no evidence of ossification of the epiphyses in the distal ends of the radii and ulnas and the pisiform bones were absent. The visual fields and fundi were normal. The basal metabolic rate was plus 6 per cent.

The blood sugar content was 425 mg. per hundred cubic centimeters on the afternoon of March 9, and the urine gave a 4 plus reaction for sugar. The patient was given a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat, with 30 units of insulin before supper and before breakfast, and the blood sugar value at 9 o'clock the next morning was 316 mg. As the condition proved difficult

to manage, she was given 8 units of insulin every three hours. These doses were reduced to 6 units every three hours, and later the injection at midnight was omitted. The diabetes was controlled by these divided doses. When the patient was again given two injections of insulin daily (40 and 30 units), the blood sugar values were high (253 mg. at 9 a. m. and 131 mg. at 2 p. m. on April 17), and the morning specimens of urine contained a little sugar. She was discharged on April 18, having gained 4 pounds (1.8 Kg.). The anterior pituitary-like gonadotropic hormone from the urine of pregnant women, followed by this hormone plus theelin, was given daily during hospitalization, without effect either in establishing the menstrual cycle or on the diabetes.

The patient was recalled to the hospital on July 11, 1934. She had increased in stature and weight (her height was 145 cm. and her weight 45.5 Kg.), and her breasts were larger and had a consistency which was more suggestive of glandular tissue. There were a few axillary hairs, and a moderate growth of pubic hair had appeared. She had not menstruated. Her general appearance was now that of a 12 to 13 year old girl. The diabetes had been fairly well managed, but she continued to show sugar in the specimens of urine taken after breakfast, and her condition still could not be controlled by two injections of insulin a day. With four injections—5 units at 3 a. m., 15 at 6 a. m., 17 at noon and 20 before supper—the blood sugar content two hours after breakfast was 147 mg. The urine was free from sugar, and there were no hypoglycemic reactions following the injection of insulin.

Case 5.—L. T., a white boy aged 17 years, was admitted to the University Hospitals on April 13, 1931, because of diabetes which had developed in 1922, when he was 8 years old. He had been given a diabetic diet and insulin (fortunately this was available for clinical use at the time) and had continued on this regimen, although sugar sometimes appeared in the urine. He had developed normally until the age of 10 years, but did not think that he had grown any since. Although he was never able to do hard work, he had had no serious illness. There was no family history of diabetes, and all the members of his family were normally developed.

The patient was underdeveloped and appeared to be about 10 years of age. He was 4 feet, 5 inches (134.6 cm.) tall and weighed 56 pounds (25.4 Kg.). There was no disproportion in relation to the trunk and extremities, and the skull and chest were of normal contour. The external genital organs were infantile, and there was complete absence of pubic hair. The physical examination revealed that he was otherwise normal except for several carious teeth and a slightly enlarged thyroid gland.

The Wassermann reaction was negative. Blood counts and determinations of the hemoglobin content were normal. Roentgenograms of the skull showed the sella turcica to be of normal size. The basal metabolic rate was minus 11 per cent.

Within the last few weeks before admission to the hospital the patient had become weaker, and the diabetes had become more severe. The sugar content of the blood on admission was 510 mg. per hundred cubic centimeters, and the urine gave a 4 plus reaction for sugar. With a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat, with insulin in doses of 15 and 7 units (before breakfast and before supper), the blood sugar content was 155 mg. at 9 a. m., but the glycosuria persisted, even when the doses of insulin were increased to 20 and 10 units. When insulin and breakfast were omitted for determination of the basal metabolic rate on April 18, the patient promptly had a severe attack of acidosis, from which he as promptly recovered when he was given 20 units of insulin with

30 Gm. of dextrose intravenously. The doses of insulin were increased to 25 and 12 units, with a resultant blood sugar content in the morning of 122 mg., but the glycosuria persisted. Early in the morning of April 22, acidosis again developed; the blood sugar content was 447 mg., and the carbon dioxide-combining power was 10 cc. per hundred cubic centimeters of blood. The patient was given his regular dose of 25 units of insulin and later was given 30 units intravenously with dextrose and sodium bicarbonate. He again recovered promptly and was able to eat his regular meal at noon. Better control of the diabetes was attained by giving insulin in divided doses, 5 units being given every three hours. A satis-

Fig. 2.—W. R., aged 19 years. The height was 155.5 cm.; the weight, 36.4 Kg. The patient had been diabetic for seven years.

factory distribution of the doses of insulin was finally achieved, and he was discharged on May 22. At this time he was receiving 5 units of insulin at 3 a. m., 7 units at 6:30 a. m., 5 units at 11:30 a. m. and 17 units before supper. The determinations of the blood sugar content on May 21 were 78 mg. at 2 p. m. and 90 mg. at 7 p. m., and on May 22 the blood sugar content was 90 mg. at 9 a. m.

Case 6.—W. R., a white boy aged 19 years, was admitted to the University Hospitals on Feb. 21, 1934. Diabetes had developed in his twelfth year. He was placed on a diet and given insulin at the time and had been receiving the same dose of insulin for six years. The urine usually showed some sugar during that time.

He complained of a recurrence of diabetic symptoms recently and had chronic diarrhea for two months preceding his admission. He had been healthy until the age of 12 years, and since then he had had no serious illness except the diabetes, but he had not grown as rapidly or been as strong as other boys. Other members of his family are of normal size, and there is no family history of diabetes.

The patient was undersized, weighing 80 pounds (about 36.4 Kg.), and appeared to be about 12 years of age. He was mentally alert, and the proportions of the body were normal. The genitalia were infantile, and there was an absence of pubic hair. The physical examination showed that the patient was otherwise normal except for punctate hemorrhages and exudates in both fundi. The visual fields were normal.

The Wassermann reaction was negative. Blood counts and the percentage of hemoglobin were normal. The protein of the blood plasma content was normal, and determinations of the cholesterol content showed 167 mg. per hundred cubic centimeters. Renal function and the urea, the uric acid and the creatinine content of the blood were normal. Urinalysis revealed glycosuria. A biopsy of material from skin and muscle revealed some arteriosclerosis. The basal metabolic rate was plus 10 per cent. Roentgenograms of the sella turcica showed it to be rather small, measuring 9 by 5 mm.

The blood sugar content on admission was 306 mg. per hundred cubic centimeters. The patient was given a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat, and the blood sugar content the next morning (at 9 a. m.) was 473 mg. Injections of insulin in doses of 60, 30 and 50 units each day failed to control the glycosuria, and the blood sugar content on March 2 (at 9 a. m.) was 455 mg. Ten units of insulin given every two hours except at midnight reduced the blood sugar content to 39 mg. As the dextrose tolerance improved, the dose of insulin was rapidly reduced to 3 units, given every two hours, the two injections at 8 and 10 p. m. being omitted. The dose was then increased to 4 units in place of 3, and with this regimen the urine was free from sugar; the blood sugar content was 112 mg. at 9 a. m. and 105 mg. at 11 p. m. (March 18). Insulin was then again given in three injections daily, in doses of 32, 3 and 20 units, and although the blood sugar values were high in the morning, they were reasonable the rest of the day. The patient was discharged on April 7, having gained 8 pounds (3.6 Kg.).

Case 7.—P. W., a white boy aged 18 years, was admitted to the University Hospitals on May 15, 1934, because of diabetes mellitus and a burning sensation of the feet and legs. Diabetes had been recognized in February 1934, with symptoms dating back to the summer of 1933. The patient was given a weighed diet and insulin by his family physician, and he gained in weight and strength for two months. The burning sensation had developed a month prior to his admission, following a cold in the head and intensification of the diabetes. For a short time the burning had involved the thighs and trunk in addition to the feet and legs. Herpes zoster had appeared on the right side of the chest but had disappeared. There were no residual symptoms, although small scars remained.

The patient was 5 feet, ¾ inches (about 154 cm.) tall and weighed 93¾ pounds (42.5 Kg.). His voice was high-pitched, and he appeared much younger than 18 years. The pubic hair was sparse, and the genitalia, especially the testicles, were small for his age. Erection of the penis was possible, but he had no desire for companionship of the opposite sex. The remainder of the physical examination revealed that he was essentially normal otherwise. No objective signs of peripheral neuritis could be found.

The Wassermann reaction was negative. The erythrocyte and leukocyte counts and the percentage of hemoglobin were normal. The results of urinalysis were negative except for sugar. The basal metabolic rate was plus 1 per cent. Roentgenograms of the skull outlined a normal sella turcica.

The patient had been taking from 90 to 115 units of insulin a day at home, and on admission to the hospital the blood sugar content was 90 mg. per hundred cubic centimeters. Without insulin and on a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat, the blood sugar content at 9 a. m. was 349 mg. With insulin in doses of 27, 5 and 15 units daily, the blood sugar values two hours after meals were satisfactory (173, 107 and 129 mg. on May 19), but the twenty-four hour specimen of urine gave a 4+ reaction for sugar, and the patient's weight decreased to 89 pounds (40.4 Kg.). On May 26, 30 Gm. of bread was added to each meal, and on June 2 the patient was given insulin in divided doses, 8 units and, later, 10 units being given every three hours except at midnight. A definite improvement in the diabetic condition resulted; the burning sensation in the feet disappeared, and the patient's weight increased to 92½ pounds (about 42 Kg.). He was discharged from the hospital on July 3. At this time he was receiving four injections of insulin daily, in doses of 12 units at 3 a. m., 20 units at 6:30 a. m., 15 units at noon and 30 units at 5 p. m. The urine was free from sugar, and the blood sugar content two hours after breakfast was 90 mg.

Case 8.—D. H., a white boy aged 16 years, was admitted to the University Hospitals on Nov. 4, 1934. A diagnosis of diabetes mellitus had been made two and a half years previously, but he had noted polydipsia and polyuria for a few months before recognition of the disease. The diabetes had been managed by diet and insulin. At the time of admission he was suffering from a recent injury to the left knee.

The boy was well nourished and well proportioned but of small stature. He was 5 feet, 1 inch (about 155 cm.) tall and weighed 96 pounds (about 43.6 Kg.). The genitalia were small and infantile in type; the pubic hair was scant, and there was no axillary hair. The left knee was stiff and swollen and contained some fluid. The other results of physical examination were negative.

The urine was normal except for the glycosuria; the Wassermann reaction was negative, and the percentage of hemoglobin and the blood counts were normal. The basal metabolic rate was plus 11 per cent. The sella turcica was small (10 by 8 mm.), and epiphyseal develpoment was delayed in both wrists.

The blood sugar content was 289 mg. per hundred cubic centimeters on admission, and he was given a diet of 70 Gm. of protein, 70 Gm. of carbohydrate and 175 Gm. of fat. Insulin in doses of 30 and 17 units (before breakfast and before supper) failed to desugarize the patient, but doses of 40 and 17 units induced a forenoon hypoglycemic reaction after a blood sugar value of 259 mg. had been noted at 9 a. m. The blood sugar content at 2 p. m. was 105 mg. The patient responded satisfactorily to treatment with four injections of insulin daily, in doses of 6 units at 3 a. m., 13 units at 6 a. m., 5 units at noon and 14 units at supper. The twenty-four hour specimen of urine was free from sugar; the blood sugar content at 9 a. m. was 152 mg., and there were no symptoms of hypoglycemic shock with this regimen. The condition of the knee cleared up after fluid had been withdrawn on two occasions. The patient was discharged on November 24.

Case 9.—E. B., a white man aged 74 years, was transferred from the surgical to the medical service on June 8, 1934, because of circulatory failure and shock following the induction of anesthesia the previous day for herniorrhaphy. There

were temporary anuria, hyperglycemia (247 mg. of sugar per hundred cubic centimeters) and glycosuria. No symptoms of diabetes had been noted previously.

The patient was 4 feet, 10 inches (147.3 cm.) tall and weighed 85 pounds (38.6 Kg.). He was well proportioned and well developed but was small in all respects. He had weighed 3 pounds (1,306.7 Gm.) at birth. All the other members of his family were of normal stature. The axillary and pubic hair was sparse, and the hair on the arms and body was less than normal. There was marked aplasia of the penis and testicles. He had never married. He had had no serious illness.

Fig. 3.—D. H., aged 16 years. The height was 155 cm.; the weight, 43.6 Kg. The patient had been diabetic for four years.

The basal metabolic rate was minus 4 per cent. Roentgenograms of the skull showed a small sella turcica. Other physical and laboratory findings were unimportant.

The patient was given 5 units of insulin every four hours and dextrose solution and saline solution intravenously until he was able to take a diabetic diet on the fourth day, when the doses of insulin were changed to 10 units before breakfast and 7 units before supper. The blood sugar content dropped to 114 mg. The patient refused to have an operation for his hernia and was discharged on a regimen of insulin, which was taken twice daily in doses of 7 and 5 units, with a restricted carbohydrate diet.

COMMENT

Of the eight young patients with infantilism who were studied, four were boys and four were girls. The ages ranged from 16 to 20 years. Diabetes developed in one boy and one girl at 8 years, in two boys and one girl at from 12 to 13 years and in one boy and two girls after the age of puberty. All had some degree of proportionate dwarfism. In two patients (girls) the infantilism was partial. All eight had severe diabetes. The two patients with partial infantilism responded to insulin and dietary control as do ordinary adults with diabetes; it was difficult to adjust the distribution of the dose of insulin for the other patients, but five of these were finally given four injections of insulin daily (beginning at 3 a. m.), and satisfactory values for the blood sugar content resulted. Six of the eight patients had received fairly efficient management in the home since the diabetic condition

Summary of Cases

Patient	Sex	Age, Years	Infantilism	Height, Cm.	Weight, Kg.	Basal Metabolic Rate, Percentage	Sella Turcica, Size in Mm.	Onset of Diabetes, Age in Years	Length of Previous Management	Final Doses of Insulin per Day in Units
D. M.	F	17	Complete	154.5	36.4	+19	9×4	15	2 yr.	3-7-4-12
E. E.	F	20	Partial	160.0	42.5	+10	12×7	20	2 wk.	17-0-10
E. W.	F	16	Partial	141.0	47.7	+15	10×7	13	2 yr.	30-0-20
E. B.	F	17	Complete	143.5	38.0	+ 6	10×8	8	9 yr.	5-15-17-20
L. T.	M	17	Complete	134.5	25.6	−11	11×7	8	9 yr.	5-7-5-17
W. R.	M	19	Complete	155.5	36.4	+10	9×5	12	7 yr.	32-3-20*
P. W.	M	18	Complete	154.0	42.5	+ 1	9×7	17	2 mo.	12-20-15-30
D. H.	M	16	Complete	155.0	43.6	+11	10×8	13	2½ yr.	6-13-5-14
E. B.	M	74	Complete	147.3	38.6	− 4	Small	?	None	7-0-5

* The blood sugar content at 9 a. m. was 253 mg., with glycosuria.

had been recognized; in fact, two patients had received insulin at the time when it first became available for clinical use. Two were seen in this hospital shortly after the diabetes developed. All but one showed ketonuria when having glycosuria; one (E. E.) had a history of recent diabetic coma and in patient L. T. acidosis quickly developed if the morning injections of insulin were omitted and as rapidly disappeared when immediate treatment was given. Two of the four girls while under treatment with sex hormones showed some temporary loss of carbohydrate tolerance. Six of the eight patients had basal metabolic rates of from plus 10 to plus 19 per cent. However, the calories per square meter of body surface per hour may represent the apparent or perhaps the physiologic age rather than the actual age in years. The case of a ninth patient, 74 years old, who had become mildly diabetic, is also reported; there was no previous history of glycosuria.

Roentgenograms either showed that the sella turcica was normal (in four patients) or outlined a sella turcica which was smaller than

normal (in five patients, including the older patient). The largest sella turcica (12 by 7 mm.) occurred in one of the patients (E. E.) with partial infantilism; the next largest (11 by 7 mm.) was present in the smallest patient (L. T.). No deformities were shown.

The data are interpreted as indicating that the dwarfism is not the result of the diabetic condition. Fliederbaum's[12] idea of an "infantilismus insulogenes" with or without diabetes mellitus which responds to insulin therapy is not confirmed by the data for our patients, since six of eight patients have received insulin treatment for from two to nine years. One must bear in mind that the glandular insufficiency may be postponed or latent and that later adolescence is possible. If one accepts the idea of a pancreatropic hormone produced by the anterior lobe of the pituitary gland (Anselmino and Hoffmann[13]), a deficiency of this hormone, together with failure of production of the gonadotropic and growth hormones, is presented. The production of hormone-inhibiting substances (Bachman, Collip and Selye[14]) may be a factor.

NOTE.—Six of these patients were reexamined in the summer and fall of 1935. Four had shown definite sexual development and increase in stature. D. M. had not changed at all. E. E. had married, had been pregnant for three months in June 1935 and went to term uneventfully. E. B. gained 4.5 cm. in height; axillary and pubic hair were present though scant; she had menstruated once, and her breasts were developed slightly. W. R. showed little change. P. W. had some growth of pubic hair with female distribution. D. H. had darker pubic hair; the genitalia were larger, and his height had increased by 3 cm.

SUMMARY

The cases of eight patients, four boys and four girls, from 16 to 20 years of age, exhibiting a syndrome of infantilism ranging from the partial to the complete type, apparently due to hypofunction of the anterior lobe of the pituitary gland, with proportionate dwarfism and severe diabetes mellitus, are reported. The coexistence of pituitary insufficiency and diabetes mellitus in these patients is not in accord with the results of recent experimental work on the interrelationship of the hypophysis as a whole and the pancreatic islet cells.

13. Anselmino, K. J., and Hoffmann, F.: Die pankreatrope Substanz aus dem Hypophysenvorderlappen; über die Darstellung und die Eigenschaften der pankreatropen Substanz, Klin. Wchnschr. **12**:1435 (Sept. 16) 1933. Hoffmann, F., and Anselmino, K. J.: Die pankreatrope Substanz aus dem Hypophysenvorderlappen; über die Stoffwechselwirkung der pankreatropen Substanz, ibid. **12**:1436 (Sept. 16) 1933.

14. Bachman, C.; Collip, J. B., and Selye, H.: Anti-Gonadotropic Substances, Proc. Soc. Exper. Biol. & Med. **32**:544 (Dec.) 1934.

BENCE-JONES' PROTEINURIA

L. MEYLER, M.D.
GRONINGEN, NETHERLANDS

The excretion of Bence-Jones' protein occupies a special position in the pathologic picture of the albuminurias. The Bence-Jones body is characterized by precipitation at a relatively low temperature (from 40 to 50 C.), followed by clearing of the solution if the heating is continued to 100 C.; on cooling the protein appears again.

By far the great majority of cases of Bence-Jones' proteinuria have been observed in association with multiple myeloma of the bone marrow. In a few instances the excretion of Bence-Jones' protein has been noticed in cases of invasion of the bone marrow by some other tumor.

The close association of this peculiar type of proteinuria with disease of the bone marrow gave rise to the question whether this body could be a product of the normal bone marrow. I therefore injected into rabbits an emulsion of cow's marrow, from which the fat had been removed by extraction with ether. Intramuscular or intraperitoneal injection of this emulsion in rabbits was followed by the production of urine which contained a small amount of protein showing the behavior of Bence-Jones' protein.

In the course of further experiments we tried to detect Bence-Jones' protein in the bone marrow itself. The marrow was extracted with ether by careful heating to remove fat. The remaining bone marrow cells were shaken with an equal volume of physiologic solution of sodium chloride and filtered. The clear filtrate showed a precipitate on heating to 60 C., which dissolved somewhat at 100 C. and reappeared on cooling. Apparently, some of the Bence-Jones' protein was contaminated with another protein. The latter substance did not redissolve at 100 C.; so the fluid did not become quite clear at this temperature. A further difficulty was encountered in the inconsistency of the results on repetition of the experiment.

So far as I am aware, Fleischer,[1] in 1880, was the first who tried to isolate Bence-Jones' protein from the normal bone marrow. Relatively little attention was paid to his communication. Magnus-Levy,[2]

1. Fleischer, R.: Virchows Arch. f. path. Anat. **80**:482, 1880.

2. Magnus-Levy, A.: Ztschr. f. klin. Med. **116**:510, 1931; **119**:307, 1932; **120**:313, 1932; **121**:533, 1932.

who in 1932 gave an admirable survey of the literature on multiple myeloma and Bence-Jones' protein, did not mention Fleischer's paper. We have repeated his work but could not reproduce his results. This may well be due to small differences in technic, but for the present we cannot deny that Thannhauser may be right in doubting the value of Fleischer's work.

Ellinger [3] and Askanazy [4] have demonstrated Bence-Jones' protein in the urine, blood and serous exudates in their cases of multiple myeloma. They also succeeded in isolating the protein from the tumors.

Their method was as follows: Emulsions of myelomatous tissue were treated with alcohol; after standing, the precipitate was shaken with distilled water. In the clear filtrate Bence-Jones' protein could be detected.

We applied this method to normal bone marrow. To obtain enough material, we used the bones of young calves, which contained hardly any fat. The marrow was expressed in a press; the resulting marrow juice was treated with two volumes of absolute alcohol and was shaken and allowed to stand for twenty-four hours. The precipitate obtained after filtration or centrifugation was mixed with an equal volume of distilled water and again allowed to stand for twenty-four hours. The resulting filtrate was almost clear and showed only slight opalescence. After the addition of a solution of sodium chloride and acetic acid a precipitate could be obtained by heating the filtrate to a temperature of from 50 to 60 C. The precipitate redissolved almost completely on further heating to 100 C. and appeared again on cooling. The reaction was perfectly reversible and could be repeated at will, which furnished the definite proof of the presence of Bence-Jones' protein in the normal bone marrow.

Most of our experiments were carried out with calf's marrow, but in a few cases we have been able to produce the same phenomenon with bone marrow obtained from man. In contrast to the results in our first experiments already described, the demonstration of Bence-Jones' protein could be constantly repeated by following Ellinger's method strictly. This author expressed the belief that after twenty-four hours all the proteins of the marrow are denatured except the Bence-Jones' protein. If the alcohol is allowed to remain in contact with the marrow juice too long, the Bence-Jones' protein is also denatured. This statement could be fully confirmed. After precipitation with alcohol the small amounts of salt present in the bone marrow itself are sufficient to dissolve the Bence-Jones' protein in distilled water.

3. Ellinger: Deutsches Arch. f. klin. Med. **62**:255, 1899.
4. Askanazy, M.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **7**:32, 1904.

The extract of bone marrow obtained in this way gives the following reactions:

1. The clear filtrate begins to flocculate after the addition of salt and acid on heating to 40 C.; at 60 C. the amount of precipitate is maximal, and at 100 C. it redissolves completely. On cooling the precipitate reappears. The protein concentration of the extract is from 3 to 4 per cent.

2. On dialysis of the extract in a Schleicher sack, the protein remains in solution and does not pass through the membrane.

3. The protein is precipitated by dilute nitric acid, sulfuric, hydrochloric, acetic and sulfosalicylic acids and tri-nitrophenol.

4. The addition of two volumes of a saturated solution of ammonium sulfate precipitates the protein completely. The same result occurs on adding an excess of a saturated solution of sodium chloride in an acid medium or on saturating the solution with magnesium sulfate.

5. The biuret, Millon, lead sulfide and xanthoproteic reactions are positive.

The peculiar behavior of Bence-Jones' protein is influenced by variations in the concentration of electrolytes in its solution. This was brought out by the excellent researches of Hopkins and Savory [5] and was confirmed in the Netherlands by Kooyman.[6] Proteins in solution show a positive electric charge on the acid side of the iso-electric point. Adsorbed positive ions increase and negative ions decrease the charge and thereby influence the stability of the protein in suspension. The valence of the ions is of great importance; generally speaking, in a slightly acid solution of Bence-Jones' protein the stabilizing (or dissolving) power of a given salt increases with the valence of its positive ion. Calcium has, therefore, a higher dissolving power for Bence-Jones' protein than sodium. The results of experiments carried out with the extracts of normal bone marrow which we used showed perfect agreement with those which Hopkins and Savory [5] obtained with Bence-Jones' protein in the urine. This may be demonstrated by the following experiment:

The bone marrow extract, as it is obtained, is slightly alkaline and is not precipitated on heating; on addition of acetic acid a precipitate is formed in the cold solution that does not dissolve on heating.

In the same way we found that sodium sulfate has a higher dispersing power than sodium chloride, but less than calcium chloride. Sodium citrate is less active because the citrate ion has a triple valence.

5. Hopkins, E. G., and Savory, H.: J. Physiol. **42**:189, 1911.

6. Kooyman, J.: Twee gevallen van Bence-Jones'sche albuminurie, Dissertation, Amsterdam, The Netherlands, 1918.

Urea has a marked promoting influence on the solubility of the protein, but not so strong an influence as that of the electrolytes. The similarity of these results and the facts known about Bence-Jones' protein offer, in my opinion, another proof of the identity of the bone marrow extract and the Bence-Jones body.

Thannhauser and Krauss [7] injected Bence-Jones' protein into rabbits, and the animals showed Bence-Jones' proteinuria. The success of these experiments is largely dependent on the quantity of protein injected, as a minimum of from about 200 to 300 mg. seems to be necessary. In a few cases these workers injected chloroform simultaneously to increase the permeability of the kidney cells.

We injected the filtrate of bone marrow into rabbits; this procedure was followed by albuminuria. A part of the protein in the urine showed

Behavior of Extract of Bone Marrow in Acid Medium

Solvent	Extract of Bone Marrow, Cc.	Water, Cc.	Behavior at 60 C.	Behavior at 100 C.	Behavior on Cooling
Sodium Chloride, Cc.					
0.2	2.5	2.3	Coagulum	Coagulum	Coagulum
0.5	2.5	2.0	Coagulum	Clearer	Coagulum
1.0	2.5	1.5	Coagulum	Clear	Coagulum
Calcium Chloride, Cc.					
0.025	2.5	2.475	Coagulum	Coagulum	Coagulum
0.050	2.5	2.450	Coagulum	Clearer	Coagulum
0.100	2.5	2.400	Coagulum	Almost clear	Coagulum
0.200	2.5	2.300	Coagulum	Clear	Coagulum
0.300	2.5	2.200	Coagulum	Clear	Coagulum
0.500	2.5	2.000	Clear	Clear	Coagulum
1.000	2.5	1.500	Clear	Clear	Clear

the properties of the Bence-Jones body. In all cases another protein was also present, which made the observation difficult. The most satisfactory method proved to be the close observation of the behavior of the urine on cooling after it had been heated to 100 C.

In addition to its presence in cases of multiple myeloma, Bence-Jones' protein has been found in cases of lymphatic and myeloid leukemia and empyema and in one instance after severe fracture of the knee. In the last instance the phenomenon is easily understood. But why should it occur in empyema and leukemia?

The substrate common to these diseases and multiple myeloma and normal bone marrow is the white corpuscles. This prompted us to investigate these cells for the presence of Bence-Jones' protein. We succeeded in detecting the substance in the pus of abscesses and empyema

7. Thannhauser, S. J., and Krauss, E.: Deutsches Arch. f. klin. Med. **133:** 183 (Aug.) 1920; **137:**257, 1921.

and also in the lymphocytes and other leukocytes in cases of leukemia. The method used was the same as that for finding the protein in the bone marrow; however, even better results were obtained after shaking the pus or the white cells with distilled water, without previous treatment with alcohol. Bence-Jones' protein was also found in the urine of a rabbit that had received injections of an extract of lymphocytes from a patient with lymphatic leukemia.

These experiments make clear why leukemia and the accumulation of pus in the body may give rise to Bence-Jones' proteinuria. The rarity of its occurrence is probably due to a quantitative factor; when the protein is found in cases of leukemia its quantity is usually small. The cause of the excretion of the protein in cases of myxedema remains obscure.

We have examined various organs for the presence of Bence-Jones' protein but could not detect it in the liver, blood plasma, thyroid, kidney and egg white or, strangely, in the spleen. Kooyman stated that he had found the substance in the liver and spleen, but his method is open to criticism. He treated the extract of these organs with a strong acid solution (30 per cent solution of acetic acid) for the detection of the protein body. In this way a precipitate was obtained that dissolved on boiling and reappeared on cooling. In the literature several communications can be found in which sulfosalicylic acid is recommended for the detection of Bence-Jones' protein. In accordance with these directions, we have also used sulfosalicylic and nitric acid; we seemed to obtain excellent results at first, until control experiments showed that in this way Bence-Jones' protein could be detected in any animal protein. If one tests a dilution of urine containing albumin from a patient with nephritis, it is easily possible to duplicate the Bence-Jones reactions by boiling the urine with sulfosalicylic acid! In my opinion, Bence-Jones' protein is not present in the organs as such, as Kooyman stated. Presumably, albumoses are formed by the treatment of protein with strong acids.

Many investigators have wondered at the sometimes enormous quantities of Bence-Jones' protein that can be excreted. They have found it hard to assume that this could all be produced by the myeloma itself. They therefore assumed that the Bence-Jones' protein was derived from the food. It has, however, been shown by Abderhalden and Rostoski [8] and in the Netherlands by Hijmans van den Bergh,[9] with the aid of precipitins, that Bence-Jones protein must be an endogenous product, which stands in a close relation to the serum proteins. According to the general opinion, Bence-Jones' protein should be a product of the

8. Abderhalden, E., and Rostoski, O.: Ztschr. f. physiol. Chem. **46**:125, 1905.

9. Hijmans van den Bergh, A. A.: Ztschr. f. klin. Med. **119**:357, 1932.

myelomatous cells. The work already described demonstrates that this substance is regularly present in the normal bone marrow; it may even be concluded that the white cells play a special part in its production.

SUMMARY

The Bence-Jones' protein is found in normal bone marrow, and it is probable that it is a part of the lymphocytes and other leukocytes. When bone marrow is broken off (in cases of tumor metastasis) or when the white cells are destroyed (in leukemia and empyema), Bence-Jones' proteinuria does not appear, as a rule, since the quantity of Bence-Jones' protein produced is too small and is, therefore, broken up in the body. In cases of multiple myeloma the white cells may have the power to produce a large quantity of Bence-Jones' protein, so much that it cannot all be destroyed and is excreted by the kidneys. This is especially true in cases of renal insufficiency.

MODIFYING EFFECT OF VARIOUS INORGANIC SALTS ON THE DIURETIC ACTION OF SALYRGAN

CLAYTON B. ETHRIDGE, M.D.

DAN W. MYERS, M.D.

AND

MARSHALL N. FULTON, M.D.

BOSTON

The use of an inorganic salt in conjunction with an organic mercurial diuretic for the purpose of augmenting diuresis was first reported by Keith, Barrier and Whelan [1] in 1925. These authors showed that a combination of ammonium chloride, administered by mouth, with injections of merbaphen may be effective in causing diuresis in patients with chronic nephritis and edema, when either substance given singly is ineffective. That ammonium chloride and certain other acid-producing salts have a diuretic action when given alone had been noted prior to that time.[2] In recent years the enhancing effect of such acid-producing salts on the diuretic response to mercurial compounds has been repeatedly confirmed. Explanations, however, of the mechanism by which these salts affect the diuretic action of mercury are still at variance.

Keith and Whelan [3] discussed certain effects which are noted when ammonium chloride is administered in conjunction with merbaphen or salyrgan: They stated: "One must conclude that an abnormal acid reaction in the tissues need not per se cause diuresis, but since it occurs when the diuretic response is most regular and marked, it must be considered a possible factor in liberating water from the tissues." Jacobs and Keith,[4] in a subsequent report, showed that ammonium nitrate is as effective as ammonium chloride with merbaphen or salyr-

From the Medical Clinic, the Peter Bent Brigham Hospital, and the Laboratory of the Department of Medicine, Harvard Medical School.

1. Keith, N. M.; Barrier, C. W., and Whelan, M.: The Diuretic Action of Ammonium Chlorid and Novasurol in Cases of Nephritis with Edema, J. A. M. A. **85**:799 (Sept. 12) 1925.

2. (*a*) Haldane, J. B. S.: Experiments on the Regulation of the Blood's Alkalinity. II, J. Physiol. **55**:265 (Aug.) 1921. (*b*) Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Action of Acid-Producing Salts, J. Clin. Investigation **1**:359 (April) 1925.

3. Keith, N. M., and Whelan, M.: A Study of the Action of Ammonium Chlorid and Organic Mercury Compounds, J. Clin. Investigation **3**:149 (Oct.) 1926.

4. Jacobs, M. F., and Keith, N. M.: The Use of Diuretics in Cardiac Edema, M. Clin. North America **10**:605 (Nov.) 1926.

gan, and the suggestion was made that the acid ions play the important rôle in furthering diuresis. In a recent summary dealing with the use of diuretics in various types of edema, Binger and Keith [5] reported on the use of ammonium chloride, calcium chloride and ammonium nitrate with merbaphen or salyrgan. They found that the salts containing chloride produce a greater and more rapid shift in the acid-base equilibrium toward the acid side than do salts containing nitrate, and they gave as their opinion that part of the diuretic effect is probably due to the change in the acid-base equilibrium. Engel and Epstein [6] studied the influence of various inorganic salts on diuresis after the administration of salyrgan. They stated that those substances which produce acidosis, as shown by a fall in the alkali reserve and a rise in the hydrogen ion concentration of the blood plasma, enhance the diuretic action of salyrgan. However, their results were not always consistent. For example, they found that calcium chloride failed to augment the diuresis from salyrgan; yet this salt has been shown by Gamble and his co-workers [7] and by others to produce acidosis. Fliederbaum and Krasucka [8] studied the response to various salts and merbaphen. They observed that the urinary output after the administration of merbaphen is augmented by the peroral administration of ammonium chloride, phosphate, nitrate and bromide, the best diuresis of all occurring with the bromide. Since these investigators found either an unchanged or a diminished response to the administration of merbaphen after the ingestion of urea, calcium chloride, hydrochloric acid, sodium bicarbonate and magnesium oxide, they concluded that the action of the ammonium salts depends on a combination of the effects of the acid anion and the urea-producing ammonium cation.

The administration of sodium chloride was reported by Goldring [9] to increase the effectiveness of merbaphen as a diuretic in two edematous patients with cardiac disease. This he attributed to elevation of a previously subnormal concentration of chlorides in the blood. Elsewhere [10] diuresis occurring after the administration of mercury salts has been considered to be "intimately associated with the available sodium

5. Binger, M. W., and Keith, N. M.: The Effect of Diuretics in Different Types of Edema, J. A. M. A. **101**:2009 (Dec. 23) 1933.

6. Engel, K., and Epstein, T.: Die Quecksilberdiurese, Ergebn. d. inn. Med. u. Kinderh. **40**:187, 1931.

7. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: Studies of Tetany: I. The Effect of Calcium Chlorid Ingestion on the Acid-Base Metabolism of Infants, Am. J. Dis. Child. **25**:455 (June) 1923.

8. Fliederbaum, J., and Krasucka, L.: Sur l'action diurétique synergétique des composés de mercure et d'ammonium, Presse méd. **40**:854 (May 28) 1932.

9. Goldring, W.: Edema in Congestive Heart Failure: Effectiveness of Diuretics as a Guide to Prognosis, Arch. Int. Med. **44**:465 (Oct.) 1929.

10. Treatment of Cardiac Decompensation, Queries and Minor Notes, J. A. M. A. **103**:858 (Sept. 15) 1934.

chloride." The ingestion of this salt was recommended in the event of a poor response to salyrgan, especially when there is a lowered concentration of chlorides in the blood. The experimental work of Evans [11] on dogs demonstrated a disappearance of the diuretic effects of salyrgan when the animals were rendered hypochloremic, with a reappearance of the response after the administration of sodium chloride. All of these observations pertained to patients or animals in a condition of hypochloremia. Evans' dogs were also dehydrated because of the loss of fluid and salt incident to a biliary fistula or the vomiting of pyloric stenosis; therefore, the initial failure of diuresis may be attributed as much to lack of available fluid for excretion as to a lack of available chlorides.

In contrast to an enhanced diuretic effect, Fliederbaum and Krasucka [8] noted a decreased response to merbaphen after the ingestion of sodium chloride. A definite inhibition of mercurial diuresis has been reported after the administration of sodium bicarbonate.[12] Engel and Epstein explained this inhibition as due to the production of alkalosis.

It is thus apparent that in the studies to which reference has been made there is no unanimity of opinion concerning the mechanism of the increase in mercurial diuresis produced by acidifying salts. There is also a paucity of information in the literature regarding the modifying effects of neutral and alkalinizing salts on the diuretic action of mercury. The present study was designed to contribute information on this subject which might elucidate some of the points of disagreement. Herein are reported the results of a series of controlled experiments carried out at weekly intervals on normal dogs to determine the modifying effect of various acidifying, alkalinizing and neutral salts on the response to the commonly used diuretic salyrgan.

PROCEDURE

Five normal adult female dogs, weighing between 15 and 22 Kg. and in good health, were utilized as the subjects for this investigation. The animals were placed on a standard daily regimen as regards the intake of food, water and salt, and in addition they were allowed 30 cc. of cod liver oil once weekly. Each dog received 35 Gm. of boiled horse meat, 30 cc. of water and 0.05 Gm. of sodium chloride per kilogram of body weight each day. The sodium chloride was administered as a 1 per cent solution by stomach tube in the morning. The water of the daily ration not consumed during the day was given by gavage at 5 p. m.

---

11. Evans, W. A., Jr.: The Effect of Changes in Salt and Water Metabolism on Salyrgan Diuresis, with Special Reference to the Effect of Permanent Bile Fistula. Medical Papers Dedicated to Henry A. Christian, Baltimore, Williams & Wilkins Company, 1936, p. 204.

12. Saxl, P., and Erlsbacher, O.: Ueber die Verstärkung der Novasurol-(Salyrgan) diurese durch Ammonium Chlorid, Wien. klin. Wchnschr. **42**:36 (Jan. 10) 1929. Engel and Epstein.[6]

No animal was subjected to more than one diuretic test per week. On the day after such an experiment each dog that had been tested was given an additional amount of water and salt (sodium chloride and, if indicated, sodium bicarbonate) to compensate, when necessary, for any excess excreted during the day of diuresis. For the remainder of the weekly interval between tests, the standard daily regimen as outlined was followed. On one or more days preceding each test day, the twenty-four hour volume of urine and the excretion of urinary chlorides were determined. Any marked variation in these figures and any evidence of abnormal thirst or diarrhea was considered sufficient ground for postponing a scheduled test on any dog. Thus, the animals were restored to approximately similar states of water and salt balance for each experiment. On the day of the test the standard daily regimen was suspended until the conclusion of the period of maximal diuresis.

At the beginning of each experiment a specimen of blood (8 cc.) was withdrawn from the leg by venipuncture. Neutral potassium oxalate was used to prevent coagulation. The bladder was then emptied by catheterization. Immediately thereafter the calculated amount of the particular salt to be studied, dissolved in 200 cc. of water, was administered by stomach tube at a single dose. On the day on which the effect of salyrgan alone was studied, as well as in the study of the effect of water alone, 200 cc. of water was given in a similar way without any dissolved salt. In the event of emesis, the vomitus was promptly readministered by tube. Nothing further by mouth was permitted the animal during the next six hours.

The output of urine was determined by catheterization at hourly intervals for five hours. Two hours after the beginning of an experiment salyrgan, when given, was injected intravenously in amounts varying from 0.75 to 1 cc., according to the weight of the animal. Three hours after the first specimen of blood was taken, that is, one hour after the time for the injection of salyrgan, a second specimen of blood was obtained. At the end of six hours the daily ration of food and water less the previously administered 200 cc. of water was given. The volume of urine excreted during the twenty-four hour period after the start of the test was determined by catheterization the next morning.

Determinations of the chloride content were carried out on whole blood and on urine after the method of Patterson, as modified by Hald.[13] The carbon dioxide-combining power of the blood plasma was determined by the method of Van Slyke and Cullen.[14] All determinations were made in duplicate.

A total of sixty-seven experiments was carried out as described and may be grouped as follows: (*A*) Experiments to determine the effect of salyrgan alone. Each of the five animals was tested in this manner. (*B*) Experiments to determine the effect of salyrgan in conjunction with nine salts: ammonium chloride, calcium chloride, ammonium nitrate, calcium nitrate, potassium chloride, sodium chloride, potassium acetate, potassium bicarbonate and sodium bicarbonate. One acid, phosphoric acid, was also tested with salyrgan. Each of these experiments was performed on four different dogs. (*C*) Experiments to determine the effect of four salts and of water without salyrgan. The salts studied in this manner were ammonium nitrate, ammonium chloride, sodium chloride and sodium bicarbonate. Each of these experiments was performed on four different dogs.

"Equivalent amounts" of the different salts studied on the test days were given in all cases. The amount of ammonium chloride used was placed arbitrarily at

13. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 838.

14. Peters and Van Slyke,[13] p. 251.

0.209 Gm. per kilogram of body weight, and with this as a basis the amounts of the other substances given were determined by reference to their molecular weights. Thus, the seven salts composed solely of monovalent ions were administered in equimolar doses. Two acid-forming salts (calcium chloride and calcium nitrate) contained a bivalent ion; the equivalent doses of these salts were calculated as one-half the equimolar amount. In the case of phosphoric acid a molar solution was considered to have, after ingestion, 1.8 times the base-binding capacity of a molar solution of ammonium chloride,[2b] and the dose was computed accordingly.

We were unable to carry out similar experiments with hydrochloric acid, owing to the intractable vomiting which followed its administration in equivalent doses. The use of sulfates was not attempted because the diarrhea which frequently follows their ingestion would interfere with the interpretation of the results.

In order to clarify the procedure followed in each of the experiments, a sample protocol is here given:

Dog 7.—A bitch police dog; weight, 21.5 Kg.

March 22, 1935, a.m., 9:27: First specimen of blood, 8 cc., withdrawn from a vein in the leg and oxalated. Chlorides, 299 mg. per hundred cubic centimeters of blood; carbon dioxide-combining power of the plasma, 46.7 volumes per cent.

9:29: Catheterization. Previous twenty-four hour volume of urine, 950 cc.; twenty-four hour urinary excretion of chlorides, 1.13 Gm.

9:31: Calcium chloride, 4.65 Gm., dissolved in 200 cc. of tap water, administered by stomach tube.

10:31: Catheterization, 28 cc. of urine.

11:32: Catheterization, 23 cc. of urine.

11:33: Salyrgan, 1 cc., injected intravenously.

p.m. 12:30: Second specimen of blood, 8 cc. Chloride content of the blood, 326 mg.; carbon dioxide-combining power of the plasma, 37.8 volumes per cent.

12:33: Catheterization, 226 cc. of urine.

1:31: Catheterization, 236 cc. of urine.

2:31: Catheterization, 143 cc. of urine. Total volume of urine for the three hour period of diuresis, 605 cc.; three hour urinary excretion of chlorides, 4.59 Gm.

3:33: Boiled horse meat, 753 Gm., and water, 445 cc., placed in cage.

March 23, 1935, a.m., 9:30: Catheterization. Remainder of twenty-four hour urine, 650 cc.; total twenty-four hour volume of urine excreted, 1,306 cc.; urinary excretion of chlorides for twenty-four hours, 5.284 Gm.

11:00: Boiled horse meat, 753 Gm.; water, 645 cc., and sodium chloride, 1.07 Gm. given (standard daily ration).

p. m. The animal given additional sodium chloride, 4 Gm., and water, 1,200 cc., to restore loss on the previous day.

The results of the experiments are set forth in the three accompanying tables. Every figure given is an average of the results for four different animals. The individual results obtained for each dog were in conformity with the averages, except for the several instances mentioned in the text. Therefore, averages are reported for the sake of brevity and simplicity.

The effects of the various salts were determined by comparison with the experiments in which salyrgan alone was given. It was found that when salyrgan was administered the diuresis was most marked during the succeeding three hours, that is, the third, fourth and fifth hours of the test. After that a rapid decline in the urinary output occurred. We therefore selected the volume of urine excreted during this three hour period of maximal diuresis as the basis for comparison, because it best showed the relative diuretic efficacy of the substances. It may be said, however, that in every case the amount of urine excreted in twenty-four hours was found to vary in the same direction as the amount excreted in three hours, though to a less striking degree.

The effects of the various substances on the carbon dioxide-combining power of the plasma and on the concentration of chlorides in the whole blood are reported as the change from the levels at the start of the experiments to those found three hours later. This method of denoting alteration in the blood has been chosen in order to simplify the presentation. The "initial" levels observed at the start of the experiments showed only slight variations from one test day to another, the probable variation [15] in any animal from its average level not exceeding 3 volumes per cent for the carbon dioxide-combining power of the plasma and 6 mg. per hundred cubic centimeters for the chloride content of the blood. We found that in our hands the experimental error of the analytic methods employed was of the same degree. In the interpretation of the results, changes in these determinations were not considered significant unless they were in excess of the experimental error.

EXPERIMENTS WITH SALYRGAN

The ten substances given with salyrgan may be arranged in three groups according to their effect on the acid-base equilibrium after ingestion and absorption. Accordingly, the presentation of the results of these tests is divided into three sections, dealing with acidifying, alkalinizing and neutral salts.

1. Acidifying Salts (table 1).—Phosphoric acid and four acid-forming salts (ammonium chloride, calcium chloride, ammonium nitrate and calcium nitrate) were tested in combination with salyrgan in a series of twenty-one experiments. Without exception there resulted a marked increase in the volume of urine excreted as compared with the tests in which salyrgan alone was used. The average *surplus* in the three-hour volume ranged from 115 cc. (58 per cent) with phosphoric acid to 320 cc. (193 per cent) with ammonium chloride. Also, in every instance there occurred a significant drop in the carbon dioxide-combining power of the plasma, ranging from an average

15. Knowlton, A. A.: Physics for College Students: An Introduction to the Study of the Physical Sciences, New York, McGraw-Hill Book Company, 1928 p. 44.

decrease of 8 volumes per cent with calcium nitrate to 15 volumes per cent with ammonium nitrate. The concentration of chlorides in the blood rose definitely in the experiments in which ammonium and calcium chloride were used. With the other acidifying salts and with salyrgan alone, the changes in the chloride content of the blood were slight and not consistent. In addition to the augmentation of the urinary output, a marked increase in the excretion of urinary chlorides for the three-hour period over that obtained when salyrgan alone was given was found in all these experiments. The excretion of chlorides was, of course, greatest in those cases in which a chloride salt was given.

TABLE 1.—*Average Effect of the Administration of Salyrgan Combined with an Acidifying Salt Compared with the Effect of Salyrgan Alone*

Salt Given at Start of Experiment	Dogs Used, No.	Volume of Urine for 3 Hours After Administration of Salyrgan, Cc.	Surplus of Urinary Volume After Administration of Salt and Salyrgan Over Salyrgan Alone, Cc.	Surplus Expressed as Percentage	Change in Carbon Dioxide-Combining Power from Initial Level,* Volumes per Cent	Change in Chloride Content of Blood from Initial Level,* Mg. per 100 Cc.	Urinary Output of Chloride for 3 Hours After Administration of Salyrgan, Gm.	Twenty-Four Hour Volume of Urine, Cc.
None†	4, 5, 6, 7	200	...	...	— 1	+ 5	1.443	776
Phosphoric acid	4, 5, 6, 7	315	115	58	—10	+10	1.909	1,017
None†	3, 4, 5, 7	230	...	...	— 1	+ 2	1.588	914
Calcium nitrate	3, 4, 5, 7	417	197	90	— 8	— 7	2.683	1,199
None†	3, 4, 5, 6	166	...	...	— 1	+ 7	1.251	779
Ammonium nitrate	3, 4, 5, 6	438	272	164	—15	0	2.533	1,122
None†	3, 5, 6, 7	167	...	...	— 1	+ 5	1.346	771
Calcium chloride	3, 5, 6, 7	464	297	178	—11	+25	3.726	1,166
None†	3, 4, 5, 6	166	...	...	— 1	+ 7	1.251	779
Ammonium chloride	3, 4, 5, 6	486	320	193	—12	+33	3.533	1,078

* Blood taken at the start of the experiment (initial level) and three hours later (1 hour after the administration of salyrgan).
† The figures for salyrgan alone differ according to the dogs used.

2. Alkalinizing Salts (table 2).—Twelve individual experiments were conducted in which salyrgan and salts of a strong base and a weak acid, namely, sodium bicarbonate, potassium bicarbonate and potassium acetate, were used. In ten of the twelve experiments there resulted a definite decrease in the urinary output as compared with that noted after the administration of salyrgan alone. In the other two experiments (one with potassium bicarbonate and one with potassium acetate) the three-hour volumes of urine were essentially the same as those obtained for the same animals when salyrgan alone was used. However, when the individual results were averaged, there was shown a definite

decrease in the urinary output with each of the three alkalinizing salts. The average *deficit* in the three-hour volumes of urine ranged from 93 cc. (47 per cent), when potassium acetate was given, to 103 cc. (62 per cent), when sodium bicarbonate was given, as compared with results when salyrgan alone was used. An increase in the carbon dioxide-combining power of the plasma occurred in each case, averaging 5 volumes per cent for sodium bicarbonate, 8 volumes per cent for potassium acetate and 9 volumes per cent for potassium bicarbonate. The concentration of chlorides in the blood was changed only slightly

TABLE 2.—*Average Effect of the Administration of Salyrgan Combined with an Alkalinizing or Neutral Salt Compared with the Effect of Salyrgan Alone*

Salt Given at Start of Experiment	Dogs Used, No.	Urinary Output for 3 Hours After Administration of Salyrgan, Cc.	Deficit in Urinary Volume After Administration of Salt and Salyrgan Over Salyrgan Alone, Cc.	Deficit Expressed as Percentage	Change in Carbon Dioxide-Combining Power from Initial Level,* Volumes per Cent	Change in Chloride Content of Blood from Initial Level,* Mg. per 100 Cc.	Urinary Output of Chloride for 3 Hours After Administration of Salyrgan, Gm.	Twenty-Four Hour Volume of Urine, Cc.
None†	3, 4, 5, 6	166	...	...	— 1	+ 7	1.251	779
Sodium bicarbonate	3, 4, 5, 6	63	103	62	+ 5	+ 1	0.112	701
None†	3, 4, 5, 7	220	...	...	— 1	+ 2	1.588	914
Potassium bicarbonate	3, 4, 5, 7	105	115	52	+ 9	— 9	0.400	762
None†	4, 5, 6, 7	200	...	...	— 1	+ 5	1.443	776
Potassium acetate	4, 5, 6, 7	107	93	47	+ 8	— 3	0.582	691
None†	3, 4, 5, 6	166	...	...	— 1	+ 7	1.251	779
Sodium chloride	3, 4, 5, 6	142	24	14	— 2	+21	1.873	689
None†	3, 4, 5, 6	166	...	...	— 1	+ 7	1.251	779
Potassium chloride	3, 4, 5, 6	157	9	5	— 4	+19	1.968	719

* Blood taken at the start of the experiment (initial level) and three hours later (1 hour after the administration of salyrgan).

† The figures for salyrgan alone differ according to the dogs used.

and not consistently by the administration of these salts. In every instance in which an alkalinizing salt was administered before the salyrgan the urinary excretion of chlorides for the three-hour period of diuresis was markedly decreased.

3. Neutral Salts (table 2).—The neutral salts studied were sodium chloride and potassium chloride. Eight individual tests were performed in which these salts were used with salyrgan. In four of the experiments (two with each salt) the three-hour urinary volume was greater, and in the remaining four smaller, than when salyrgan alone was used. When the figures were averaged, a slight diminution of diuresis was shown when either of the neutral salts was used, but the deficit was

not of significant degree. Measurements of the carbon dioxide-combining power of the plasma showed an average drop of 2 volumes per cent for sodium chloride and of 4 volumes per cent for potassium chloride. Determinations of the chloride content of the blood showed for each salt an average rise of about 20 mg. per hundred cubic centimeters. The three-hour urinary excretion of chlorides was markedly increased in each case without any apparent relation to the volume of urine excreted.

EXPERIMENTS WITHOUT SALYRGAN

The five substances given without salyrgan were water, sodium bicarbonate, sodium chloride, ammonium nitrate and ammonium chloride. Twenty experiments were performed, each substance being tested on the same four dogs. The results of these experiments are

TABLE 3.—*Average Results Obtained After the Administration of Water, Various Salts and Salyrgan Separately* *

Substance Given	Urinary Output for Three Hour Diuretic Period, Cc.	Change in Carbon Dioxide-Combining Power from Initial Level, Volumes per Cent†	Change in Chloride Content of Blood from Initial Level, Mg. per 100 Cc.†	Urinary Output of Chloride for Three Hour Diuretic Period, Gm.	Twenty-Four Hour Volume of Urine, Cc.
Water	35	— 1	+ 7	0.016	599
Sodium bicarbonate	45	+11	+ 9	0.042	634
Sodium chloride	54	— 2	+30	0.613	666
Ammonium nitrate	99	—13	0	0.401	743
Ammonium chloride	74	—12	+35	0.653	686
Salyrgan	166	— 1	+ 7	1.251	779

* Dogs 3, 4, 5 and 6 were used in each of these experiments.
† Blood taken at the start of experiment (initial level) and three hours later.

given in table 3 as averages. The two acidifying salts, ammonium chloride and ammonium nitrate, acting alone provoked a greater urinary output for the three-hour diuretic period than did water, sodium bicarbonate or sodium chloride and thus showed an intrinsic diuretic action of slight degree. The urinary volumes, however, were relatively small compared with those when salyrgan alone was given. With a single exception the changes in the carbon dioxide-combining power of the plasma and in the concentration of chlorides in the blood were the same for any salt, whether it was given alone or in conjunction with salyrgan. This might be expected if one notes the negligible effect of salyrgan alone on these determinations. In the case of the exception (sodium bicarbonate) a greater average rise in the carbon dioxide-combining power and in the chloride content of the blood was observed when this substance was given alone than when it was given with salyrgan. This difference occurred consistently in the individual experiments, but the reason for the discrepancy is not clear.

COMMENT

The method employed in this investigation was designed to provide a more accurate basis for determining the influence of various salts on the diuretic action of salyrgan than is usually achieved clinically. Most of the previously reported studies on this subject have dealt with clinical experience with patients under conditions that have often been dissimilar. It is our feeling that the method we have used has the following advantages:

1. Although edema constitutes the chief therapeutic indication for the use of diuretic drugs, its presence makes the comparative study of diuretic efficacy difficult. The variability of the cause and of the degree of edema is such that the capacity for diuretic response is seldom similar in different patients or in the same patient at different times. In our experiments on normal dogs this factor has been eliminated.

2. By replacement of the salt and water lost during a diuretic experiment by a standard daily intake of food, water and sodium chloride for one week, the animals were restored to relatively similar states of salt and water balance. Therefore, all the dogs possessed approximately the same capacity for diuretic response whenever tested.

3. In preliminary tests with dogs maintained on a regimen including fluids ad libitum, we observed a definite and sustained diuresis from ammonium nitrate alone if this salt was given repeatedly over a period of several days. When salyrgan was injected subsequently there was a poor diuretic response. Therefore, conclusions based on the volume of urine excreted after the injection of one diuretic (salyrgan) after partial dehydration has been produced by a prolonged administration of another diuretic (an acid-producing salt) may be misleading with regard to the true diuretic efficacy of the combination. In this investigation an "equivalent amount" of every salt studied was administered in a single large dose at such a time that its effects would be clearly manifested during the period of action of the salyrgan.

The results of the experiments show that, of the nine salts and one acid given in conjunction with salyrgan, five substances—ammonium chloride, calcium chloride, ammonium nitrate, calcium nitrate and phosphoric acid—caused marked augmentation of diuresis compared with the urinary output after salyrgan alone had been given. That this increase in diuresis was not due to a specific effect of the ammonium ion is shown by the similar results obtained with calcium chloride and calcium nitrate. That the enhanced response was not dependent on the elevation of the chloride content of the blood was demonstrated by the striking increase in the urinary output caused by the two nitrate salts, with no significant alteration in the concentration of chlorides in

the blood. The five substances which caused an augmentation of diuresis were all acidifying agents. All had one common effect when ingested, namely, the production of acidosis, as shown by a lowering of the carbon dioxide-combining power of the plasma. It seems evident, therefore, that the production of acidosis is the factor responsible for the increase in diuresis which occurs when salts of this type are given with salyrgan.

The three salts which caused a definite decrease in the response to salyrgan, potassium acetate, potassium bicarbonate and sodium bicarbonate, were all alkalinizing salts. This was true of potassium acetate with salyrgan, despite the fact that it is considered as a diuretic when used alone.[16] These three salts all had one common effect after ingestion, namely, the production of alkalosis, as shown by an elevation of the carbon dioxide-combining power of the plasma. The changes in the chloride content of the blood obtained with these salts were small and not consistent. It appears from these observations that the production of alkalosis is the factor responsible for the decrease in diuresis when salts of this type are given with salyrgan.

No significant effect on the response to salyrgan was produced by the two neutral salts sodium and potassium chloride. The absence of increased diuresis in the presence of a marked elevation of the chloride content of the blood further indicates the lack of influence of the concentration of chlorides in the blood on the extent of diuresis under the conditions employed in these experiments.

Chart 1 presents graphically the average effects of the various salts when they were given in conjunction with salyrgan. Alterations in the chloride content of the blood and in the carbon dioxide-combining power of the plasma produced by the salts with salyrgan are depicted in the upper portion. Corresponding volumes of urine excreted during the three-hour period of maximal diuresis are indicated in the lower part, and for purposes of comparison the average volumes of urine excreted after the administration of salyrgan alone are shown. The marked increase in the volumes of urine excreted after the administration of all salts causing acidosis, the absence of any effect on diuresis caused by neutral salts and the definite decrease in the urinary output after the administration of all salts causing alkalosis are apparent. No correlation between the extent of diuresis and the changes in the concentration of chloride in the blood can be discerned.

Chart 2 presents graphically the comparison between the urinary output resulting when each of four salts was given alone and that resulting from the combined action of each of these salts and salyrgan.

16. Lyon, D. M.: Observations on Diuretics and Their Uses, Brit. M. J. **2**:853 (Nov. 11) 1933.

The average volumes of urine excreted are depicted for the three-hour diuretic period after the administration of water alone, of the several salts alone, of salyrgan alone and of the salts with salyrgan. The chart illustrates particularly that the diuretic response resulting from the combined action of an acidifying agent and salyrgan is markedly in excess of the sum of the responses obtained with these substances

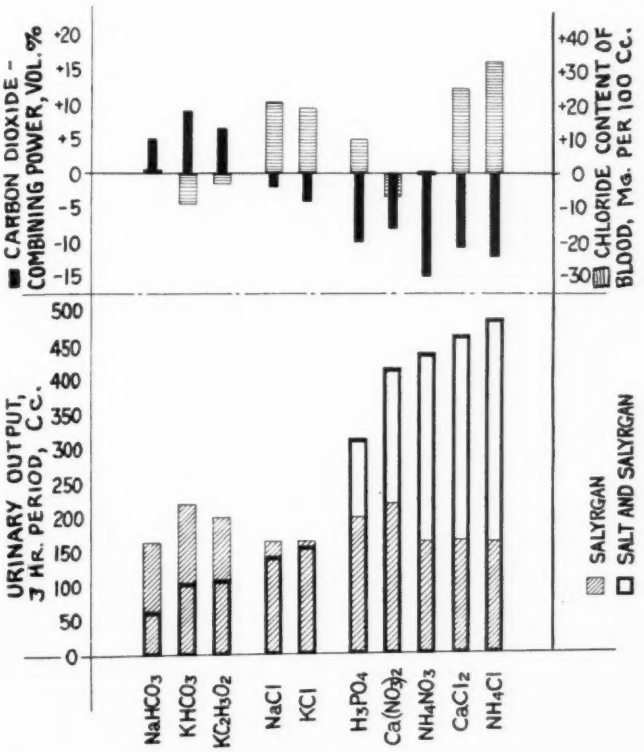


Chart 1.—Urinary output and changes in the blood resulting from the combined action of salyrgan and various salts, sodium bicarbonate, potassium bicarbonate, potassium acetate, sodium chloride, potassium chloride, phosphoric acid, calcium nitrate, ammonium nitrate, calcium chloride and ammonium chloride. Each result represents the average for four different animals. The volume of urine excreted after the administration of salyrgan alone differed according to the dogs used. The chart illustrates the correlation between the extent of diuresis and the changes in the carbon dioxide-combining power of the plasma.

when given separately. It is therefore apparent that a synergistic diuretic action occurs when one of these acidifying salts and salyrgan

act concurrently. The virtual absence of any modifying effect on the diuresis due to salyrgan when a neutral salt (sodium chloride) is given is also shown. Moreover, it may be observed in this chart that the urinary output after the administration of sodium bicarbonate in conjunction with salyrgan exceeded but slightly the output when this salt alone was used. It is thus indicated that an almost complete inhibition of the diuretic action of salyrgan may occur when an alkalinizing salt is given with salyrgan.

Blumgart and his associates [17] stated that the action of ammonium nitrate and salyrgan when given together represented a simple addition of the effects of the two substances. Keith and Whelan [3] suggested that

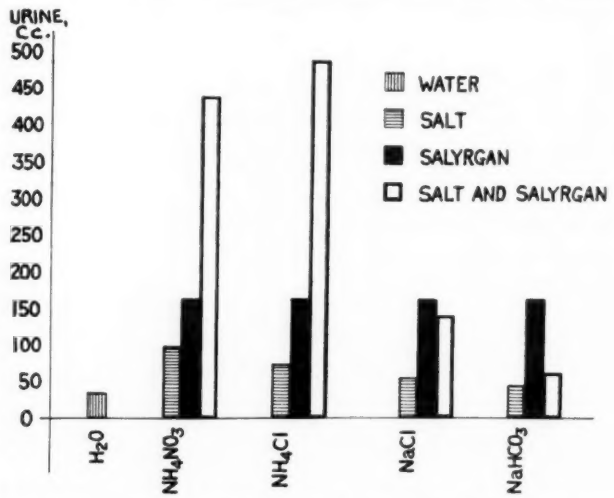


Chart 2.—Urinary output resulting from the administration of water alone and of salyrgan and various salts (ammonium nitrate, ammonium chloride, sodium chloride and sodium bicarbonate) given separately and in combination. Each result represents the average volume excreted during a three hour period by the same four animals.

the combined action of ammonium chloride and organic mercurial compounds may be simply cumulative. Our results are not in keeping with these conclusions. On the contrary, they indicate that in normal dogs an acidifying salt and salyrgan acting concurrently have a synergistic diuretic action which gives rise to a urinary output far in excess of the sum of their separate effects.

17. Blumgart, H. L.; Gilligan, D. R.; Levy, R. C., and Brown, M. G.: The Effect of Diuretics on Water and Salt Metabolism, Tr. A. Am. Physicians **47**:304, 1932.

Certain points of clinical interest are brought out by these studies. In the first place, when an acidifying salt is given with salyrgan it should be administered in sufficiently large doses and at such times as to afford the maximal acidifying effect during the time of action of the salyrgan. It is suggested by the work of Dennig, Dill and Talbott [18] that this desired effect is not best obtained by the continuous administration of such a salt. These authors showed that in a person who took large amounts of ammonium chloride daily the degree of acidosis was more marked on the second and third days of administration than subsequently. This occurred even though ingestion of the salt was continued. The single dose method employed in our study is not strictly applicable to the treatment of patients. Most human beings would not tolerate in one dose a quantity of acidifying salt comparable to the amounts given in these experiments. However, it appears advantageous to administer to patients fairly large amounts of an acidifying salt for the two days preceding and on the day of the mercurial injection rather than to give the salt continuously. Such a program was found effective by Saxl and Erlsbacher.[12] We do not wish to imply that all the acidifying agents employed in this study are necessarily of equal value for clinical use. The observations that acidosis is more easily produced, in human beings at least, with ammonium chloride than with ammonium nitrate [19] and that methemoglobinemia occasionally occurs as a toxic manifestation with the nitrate [20] lead us to prefer ammonium chloride for clinical use, in spite of its more disagreeable taste. Again, it seems evident that acidifying salts are distinctly more efficacious than neutral salts, such as sodium chloride, in increasing the diuretic response to salyrgan. In our experiments on dogs which were maintained in a normal state, the administration of sodium chloride caused no significant effect on the diuresis produced by salyrgan. This result does not contradict the observations of others that sodium chloride may be effective in increasing the response to mercurial diuretics in the presence of hypochloremia. The conditions are not comparable in the two cases. However, our findings suggest that even in the presence of hypochloremia a chloride salt which can produce acidosis, such as ammonium chloride, might well be administered in preference to sodium chloride for the purpose of enhancing the diuretic action of salyrgan. Finally, because

18. Dennig, H.; Dill, D. B., and Talbott, J. H.: Bilanzuntersuchung einer Salmiakazidose, Arch. f. exper. Path. u. Pharmakol. **144**:297, 1929.

19. Keith, N. M.; Whelan, M., and Bannick, E. G.: The Action and Excretion of Nitrates, Arch. Int. Med. **46**:797 (Nov.) 1930. Binger and Keith.[5]

20. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, J. A. M. A. **91**:2060 (Dec. 29) 1928. Tarr, L.: Transient Methemoglobinemia Due to Ammonium Nitrate, Arch. Int. Med. **51**:38 (Jan.) 1933.

of their inhibiting effect on the response to salyrgan, basic or alkalinizing salts should not be given to patients who are receiving mercurial diuretics.

SUMMARY

Normal dogs, under controlled conditions, were tested to determine the comparative diuretic responses resulting from the administration of salyrgan alone, of salyrgan in conjunction with various inorganic salts and of several of these salts alone.

Four acidifying salts (ammonium chloride, calcium chloride, ammonium nitrate and calcium nitrate) and phosphoric acid when given with salyrgan effected a marked increase in the diuresis as compared with the response obtained from salyrgan alone. A lowering of the carbon dioxide-combining power of the plasma was associated with the enchancement of the diuresis in each case.

Three alkalinizing salts (potassium acetate, potassium bicarbonate and sodium bicarbonate) when given with salyrgan produced a definite decrease in the urinary output as compared with that after the administration of salyrgan alone. In each instance a rise in the carbon dioxide-combining power of the plasma was demonstrated.

Two neutral salts (sodium and potassium chloride) when given with salyrgan caused no appreciable change in the diuretic response as observed after the administration of salyrgan alone, and the level of the carbon dioxide-combining power of the plasma was not sufficiently altered by their administration.

The differences in the response of salyrgan produced by the administration of the various salts showed no apparent relation to coincidental changes in the level of the chloride content of the blood.

A synergistic diuretic action was shown to occur when an acidifying salt and salyrgan acted concurrently. The resulting diuresis was far in excess of the sum of the urinary volumes obtained when the acidifying salt and salyrgan were given separately. Conversely, a marked inhibition of the diuretic action of salyrgan was noted when an alkalinizing salt and salyrgan acted at the same time.

It is concluded that the modifying effect of various inorganic salts on the diuretic action of salyrgan is dependent on the acidosis or alkalosis which the salts produce on administration.

THE NONSPECIFIC RÔLE OF PRESSOR SUBSTANCES IN THE PLASMA OF HYPERTENSIVE PATIENTS

LOUIS LEITER, M.D., PH.D
CHICAGO

The etiology of clinical hypertension is still unknown. Very little has been added to the knowledge of the subject since Janeway's masterly reviews in 1904[1] and 1913.[2] The center of interest has shifted from the rôle of the kidneys to the influence of hyperirritable vasomotor centers, inadequate depressor reflexes (carotid sinuses and aorta), excessive or unbalanced action of chemical pressor substances in the circulating blood, physicochemical changes in the arteriolar media (premature "aging"?)—in short, all the possible physiologic mechanisms involved in the regulation of blood pressure. To complete the circle, the kidneys have again been placed in the foreground by the recent ingenious experiments of Goldblatt and his associates.[3] Their results are particularly significant because for the first time hypertension has been produced in the experimental animal by obstruction of the renal arteries without the necessary association of renal insufficiency.

The difficulty of analyzing the actual nature of the disturbance of the blood pressure-regulating mechanism in hypertensive patients is obvious. For the present one can only speculate on the state of irritability of the vasomotor center or centers or of the carotid sinuses and aortic nerve endings. Emphasis on the hereditary and constitutional aspects of hypertension adds relatively little to the knowledge of the etiology of the condition and rather definitely discourages experimental studies. For these reasons, any attempt to explain certain types of hypertension on the basis of a simple mechanism, objectively demonstrable, warrants serious consideration and careful repetition, even though the underlying assumptions may not be acceptable. Therefore, the present study is the direct result of the publications by Bohn and

From the Lasker Foundation for Medical Research and the Department of Medicine, the University of Chicago.

1. Janeway, T. C.: The Clinical Study of Blood Pressure, New York, D. Appleton & Company, 1904.

2. Janeway, T. C.: Nephritic Hypertension: Clinical and Experimental Studies, Am. J. M. Sc. **145**:625, 1913.

3. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**:347, 1934.

his associates,[4] who have submitted evidence to substantiate the claim of Volhard [5] that the "pale" forms of hypertension (malignant nephrosclerosis, acute diffuse glomerulonephritis and eclampsia gravidarum) are associated with, and probably the result of, the presence of chemical pressor substances in the blood which are not present in the "red," or benign, types of hypertension.

The method of procedure differed in several important particulars from the technic employed by Bohn or by subsequent investigators. Instead of preparing alcoholic extracts of whole blood or plasma, heparinized plasma was used, on the general principle that the less artificial treatment the blood received the more likely it would resemble the circulating blood of the patient. Regardless of the theory of pressor action, i. e., whether it is due to an excess of pressor substance or to a decrease of the normal depressor substances, whole plasma should represent the actual condition in the patient much more accurately than an extract. To surmount the difficulty of dilution of plasma of human blood by the recipient animal's blood volume, the rat was chosen as the test object instead of a larger animal. The importance of controlling the many variables in this type of investigation was clearly recognized from the beginning.

METHODS

Venous blood, about 15 cc., was drawn shortly before noon from an antecubital vein of the patient into a syringe containing 1 cc. of a 1 per cent solution of heparin in physiologic solution of sodium chloride. The blood was transferred to a 15 cc. centrifuge tube and centrifugated. The time that elapsed between the drawing of the blood and the injection of the plasma into a rat was usually not more than three and one-half hours.

White rats, weighing about 300 Gm., were used in the experiments. Anesthesia was induced with sodium barbital, given subcutaneously from one and one-half to three hours before the experiment. The dose varied from 5 to 44 mg. but was usually from 10 to 20 mg. The rat was kept warm. A hypodermic needle was introduced into an exposed but unligated vein on the anterior aspect of the thigh, and from 10 to 12 mg. of heparin in 0.5 cc. of saline solution was injected. The needle was left in the vein but was occluded between injections with a stylet passed through a small cork that fitted the hub of the needle snugly. A tuberculin syringe with a capacity of 1 or 2 cc. was attached to the needle for

4. (*a*) Bohn, H.: Untersuchungen zum Mechanismus des blassen Hochdrucks: Gefässverengernde Stoffe im Blute beim blassen Hochdruck, Ztschr. f. klin. Med. **119**:100, 1931. (*b*) Bohn, H., and Schlapp, W.: Untersuchungen zum Mechanismus des blassen Hochdrucks: Weitere Erfahrungen über den Nachweis pressorischer Stoffe im Blute beim blassen Hochdruck, ibid. **127**:233, 1934.

5. Volhard, F.: Die doppelseitigen hämatogenen Nierenerkrankungen, in von Bergmann, C., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 1, chap. 4.

each injection. The rate of injection was usually from 1 to 1.5 cc. per minute, and the volume given in a single injection was usually 1 or 2 cc. The interval between injections was usually from five to fifteen minutes.

The blood pressure was recorded from the right common carotid artery by means of a needle cannula connected through an adapter with the rubber tubing of the mercury manometer. The needle cannula was a gage 20 needle cut down to 1 cm., with the point smoothed off and the end surmounted with a bit of solder to keep the ligature from slipping.[6] The solder, however, was later found to be unnecessary, and its absence facilitated the cannulation of the artery without trauma. Physiologic solution of sodium chloride was used in the manometer tubing. The injection of a little of the solution into the lumen of the rubber tube, when the column of blood rose into the small piece of glass tubing near the adapter, was helpful in preventing coagulation and in dislodging small clots in the needle. Gentle squeezing of the rubber tube was also helpful in forcing clots out of the cannula, but serious depressor reflexes at times resulted from these maneuvers. With proper technic, tracings of the blood pressure could be obtained in many experiments over periods as long as two hours.

Artificial respiration, when necessary, was administered through a bent gage 16 needle, 3½ inches (9 cm.) long, inserted in the trachea and connected with the compressed air outlet. The rate and depth of respiration were controlled manually.

Each rat was killed at the conclusion of the experiment, and the condition of the heart, lungs and abdominal vascular bed was noted carefully.

RESULTS

Under the conditions of the procedure just outlined, the rats were only lightly anesthetized during the first hour of the experiment and responded readily to vasomotor stimuli. The mere attachment of the syringe to the needle in the vein of the thigh often initiated a depressor reflex lasting twenty or thirty seconds. A less frequent effect was a pressor reflex. Occasionally the depressor reflex led to a striking fall in the blood pressure and typical vasomotor shock. Intravenous injections of heparinized plasma or other solutions were usually withheld until the reflex changes incidental to manipulation of the needle had subsided. In all instances the figures for rises in blood pressure were calculated from the control level noted just prior to the mechanical reflex, even though the injection was started, in some instances, during the subnormal level of blood pressure of the depressor reflex.

The control blood pressure of this series of 131 rats varied considerably. However, 69 per cent of the initial values fell between 101 and 140 mm. of mercury, 20 per cent were above 140 mm., and only 11 per cent were below 101 mm. The largest portion, 40 per cent, had an initial value for blood pressure between 121 and 140 mm. The amount of sodium barbital used for anesthesia did not materially influence the distribution of the control levels of blood pressure within the

6. Durant, R. R.: Improvised Metal Cannula, J. Lab. & Clin. Med. **12**:1011, 1927.

range employed, although it did seem to affect the rat's response to injected plasma. This feature will be discussed later.

The clinical material represented in these experiments consists of observations on 117 subjects, among which were included persons with various types of hypertension (primary, arteriosclerotic and renal) and a small group of nonhypertensive subjects. Table 1 shows the clinical subdivisions. While the criteria for differentiation of the various groups are somewhat arbitrary, they conform to the prevailing clinical usage. The term "malignant" hypertension is used as the synonym for "pale" hypertension, to include both the primary and the nephritic type, or those cases in which hypertension and its consequences determine the malignant tempo of the disease. Such terminology is admittedly open to serious criticism (as is the whole concept of "malignant" hyperten-

TABLE 1.—*Distribution of the Clinical Material and the Plasmas Causing Pressor Effects in the Various Groups*

Diagnosis	Number of Subjects	Plasmas Causing Pressor Effects	
		Number	Percentage
A. Primary hypertension			
1. Uncomplicated	26	10	39
2. With myocardial or coronary disease	23	8	35
3. With cerebral vascular disease	12	8	67
Total	61	26	43
B. Arteriosclerotic hypertension	13	6	46
C. Nephritic hypertension	9	5	56
D. "Malignant" hypertension*	17	6	35
E. Miscellaneous conditions, nonhypertensive	17	8	47
Grand total	117	51	44

* This group includes subjects with both primary and nephritic hypertension.

sion), but it is valid for the purposes of this investigation, since Bohn has found pressor substances most constantly in the plasma of these patients.

The general effect on the rat's blood pressure of the intravenous injection of heparinized human plasma was variable, but in only 5 animals was there a "toxic" result in the form of immediate cardiac or vasomotor depression, which occurred with each injection. In all of these rats the blood pressure began to fall during the injection, an occurrence not observed in other rats except as a rare manifestation of a markedly increased blood volume after repeated injections. Apart from these 5 rats, all the others tolerated the single injection of 1 or 2 cc. of plasma, and often repeated injections, without untoward effects, provided that respiration was adequate. The immediate response of the blood pressure varied from no change to a definite rise of 6 mm. of mercury or more during the injection, followed by a return to the control level within a minute or two. In many instances there was an

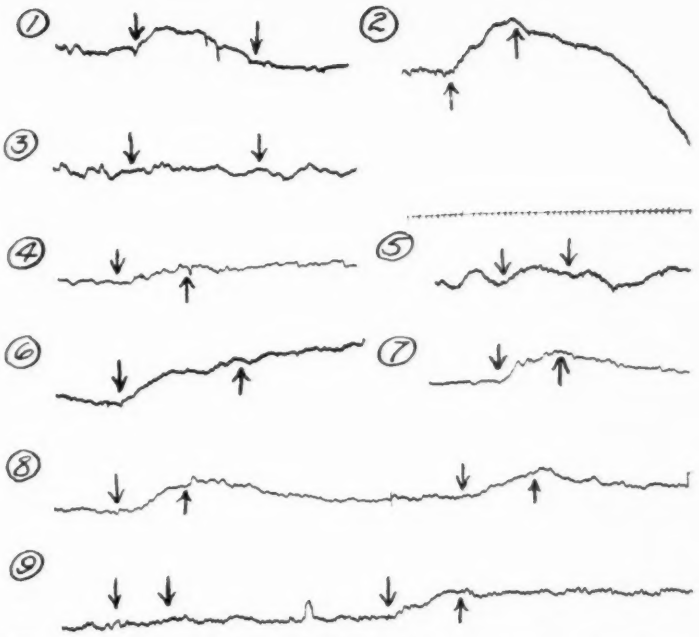


Fig. 1.—*1* (MD; rat 113). Control B. P., 114 mm.; 8 mm. rise from 2 cc. of plasma injected in ninety-eight seconds.

2 (MD; rat 62). Control B. P., 100 mm.; 15 mm. rise from 1 cc. of plasma injected in fifty-three seconds. Note the late toxic effect.

3 (MH; rat 101). Control B. P., 132 mm.; no effect from 2 cc. of plasma injected in one hundred seconds.

4 (MH; rat 76). Control B. P., 130 mm.; 4 mm. rise (?) from 1 cc. of plasma injected in sixty-eight seconds.

5 (MH; rat 26). Control B. P., 98 mm.; no effect from 2 cc. of plasma injected in forty-two seconds.

6 (UH; rat 106). Control B. P., 135 mm.; "sustained" 14 mm. rise from 2 cc. of plasma injected in one hundred and fifteen seconds.

7 (HC; rat 61). Control B. P., 114 mm.; 8 mm. rise from 1 cc. of plasma injected in forty-five seconds.

8 (HH; rat 69). Control B. P., 111 mm.; 11 mm. rise from 1 cc. of saline solution injected in fifty-seven seconds. Eleven minutes later the control B. P. was 115 mm.; 8 mm. rise from 1 cc. of plasma injected in sixty-four seconds.

9 (HC; rat 161). Control B. P., 120 mm.; no effect from 1 cc. of saline solution injected in fifty-seven seconds. Five minutes later the control B. P. was 120 mm.; "sustained" 9 mm. rise from 1 cc. of plasma injected in fifty-five seconds.

In the legends for figures 1 and 2 the abbreviations MD, MH, UH, HC, HH, and NH have the diagnostic meaning indicated in the footnote to table 2. The tracings read from left to right. The arrows indicate the beginning and the end of an injection. The term plasma denotes heparinized plasma. B. P. denotes blood pressure.

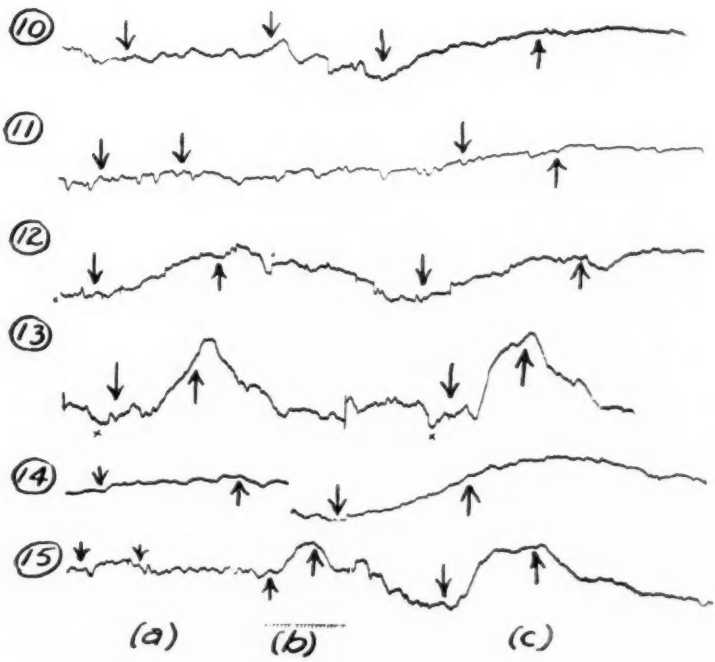


Figure 2

EXPLANATION OF FIGURE 2

Fig. 2.—*10* (HC; rat 142). Control B. P., 128 mm.; no effect from 2 cc. of saline solution injected in one hundred and thirty-two seconds. Ten minutes later the control B. P. was 131 mm.; "sustained" 15 mm. rise from 2 cc. of plasma injected in one hundred and thirty-five seconds.

11 (MH and MD; rat 167). Control B. P., 112 mm.; no effect from 1 cc. of MH plasma injected in seventy seconds. Five minutes later the control B. P. was 112 mm.; "sustained" 8 mm. rise from 1 cc. of MD plasma injected in seventy seconds.

12 (MH; rat 117). Control B. P., 104 mm.; 12 mm. rise from 2 cc. of saline solution injected in one hundred and ten seconds. Eighteen minutes later the control B. P. was 104 mm.; "sustained" 15 mm. rise from 2 cc. of plasma injected in one hundred and fifteen seconds.

13 (NH; rat 86). Control B. P., 146 mm.; 21 mm. rise from 1 cc. of epinephrine (0.0005 mg.) in plasma injected in seventy seconds. Nine minutes later the control B. P. was 145 mm.; 23 mm. rise from 1 cc. of epinephrine in saline solution injected in eighty seconds.

14 (MH; rat 134). Control B. P., 132 mm.; 4 mm. rise (?) from 2 cc. of plasma injected in one hundred and twenty-five seconds. Twenty-one minutes later the control B. P. was 72 mm.; 16 mm. rise from 2 cc. of plasma injected in one hundred and thirty seconds.

15 a and *b* (NH; rat 53). Control B. P., 126 mm.; no effect from 1 cc. of plasma injected in fifty-eight seconds. Thirty-three minutes later the control B. P. was 80 mm.; 9 mm. rise from 1 cc. of plasma injected in fifty-four seconds. *c* (NH; rat 50). Control B. P., 64 mm.; 19 mm. rise from 2 cc. of plasma injected in one hundred and two seconds. At 131 mm. (not illustrated) a "sustained" rise of 8 mm. occurred.

TABLE 2.—*Typical Experimental Results in Relation to the Clinical Diagnosis and the Reactivity of the Rat*

Patient	Age	Diagnosis*	Rat	Plasma†		Saline Solution†		Epinephrine in Saline Solution‡		Epinephrine in Plasma‡		Comment
				Control Blood Pressure, Mm. Hg	Pressor Effect	Control Blood Pressure, Mm. Hg	Pressor Effect	Control Blood Pressure, Mm. Hg	Pressor Effect	Control Blood Pressure, Mm. Hg	Pressor Effect	
M. R.	52	UH	34A	131	0(2)	...	.....	126	24(0.5,1M)	97	20(1,2M)	
A. S.	58	UH	47	149	0(1)	...	.....	...	.....	...	.....	Both carotids ligated
L. W.	19	UH	64	122	0(1)	...	.....	121	7(1,4M)	120	9(1,4M)	
H. R.	47	UH	95	154	11(2)	146	18(2,S)	110	10(2,4M)	153	11(2,4M)	Saline solution injected first
I. S.	33	UH	106	135	14(2,S)	138	4(2)	128	10(2,4M)	139	12(2,4M)	Saline solution injected first
J. K.	49	HH	45	133	0(1)	...	.....	129	11(0.5,2M)	131	9(1,4M)	
H. D.	58	HH	87	130	12(1)	134	10(1)	132	13(1,2M)	135	13(1,2M)	Plasma injected first
M. S.	52	HH	120	121	0(2)	112	6(2,S)	...	.....	108	11(1,2M)	Saline solution injected first
J. D.	48	HH	151	90	8(2)	68	11(2,S)	90	20(1,2M)	...	.....	Saline solution injected first
A. F.	63	HH	158	138	0(1)	144	0(2)	...	.....	...	.....	Saline solution injected first
A. S.	47	HC	35	126	4(2)	...	.....	...	.....	...	.....	
H. A.	58	HC	61	114	8(1)	116	0(1)	...	.....	...	.....	Plasma injected first
F. C.	65	HC	90	138	18(2,S)	142	14(2,S)	143	6(1,2M)	146	14(2,4M)	Saline solution injected first
D. B.	54	HC	131	160	10(2)	129	0(2)	...	.....	127	9(2,4M)	Plasma injected first
M. S.	62	AH	88	126	8(1)	134	4(1)	122	11(1,2M)	122	13(1,2M)	Saline solution injected first
E. N.	73	AH	119	112	10(2,S)	121	6(2)	...	.....	116	8(2,4M)	Saline solution injected first
W. S.	78	AH	128	120	0(2)	123	0(2)	...	.....	106	6(2,4M)	Saline solution injected first
H. D.	62	AH	157	136	0(2)	136	0(1)	...	.....	...	.....	Saline solution injected first
F. R.	41	NH	21	190	0(2)	...	.....	...	.....	108	34(2,1M)	
R. S.	26	NH	65	126	12(1)	126	7(1,S)	110	6(1,4M)	121	8(1,4M)	Saline solution injected first
E. B.	51	NH	85	140	6(1,S)	148	0(1)	144	20(1,2M)	148	21(1,2M)	Plasma injected first
G. S.	28	NH	132	155	11(2)	130	20(2,S)	...	.....	132	8(2,4M)	Saline solution injected first
G. B.	30	NH	166	148	7(1)	140	0(1)	...	.....	...	.....	Saline solution injected first
L. P.	22	MH	44	138	0(1)	138	0(1)	138	18(1,2M)	...	.....	Plasma injected first
C. B.	46	MH	57	114	9(1)	104	0(1)	...	.....	...	.....	Plasma injected first
N. D.	43	MH	76	130	4(1)	...	.....	130	14(1,2M)	...	.....	Plasma injected first
R. G.	32	MH	153	109	11(2)	112	6(2)	99	14(1,2M)	86	23(2,2M)	Saline solution injected first
C. D.	41	MH	167	114	0(2)	108	0(1)	...	.....	...	.....	Saline solution injected first
D. S.	30	MD	39	120	5(2)	...	.....	126	8(1,2M)	126	14(1,2M)	Plasma injected first
A. L.	46	MD	62	100	15(1)	111	9(1,S)	...	.....	...	.....	Saline solution injected first
F. H.	43	MD	113	114	8(2)	...	.....	...	.....	...	.....	
J. H.	41	MD	160	156	7(2)	156	0(1)	...	.....	...	.....	Saline solution injected first
J. W.	52	MD	164	142	0(1)	142	0(1)	139	15(1,2M)	...	.....	Saline solution injected first

* In this and the following tables UH stands for uncomplicated primary hypertension; HH, for primary hypertension with myocardial or coronary disease; HC, for primary hypertension with cerebral vascular disease; AH, for arteriosclerotic hypertension; NH, for nephritic hypertension; MH, for malignant hypertension, and MD, for miscellaneous nonhypertensive disease.

† In this and the following tables numerals in parenthesis indicate the number of cubic centimeters injected. The letter S stands for sustained effect.

‡ In this and the following tables the first numeral in parenthesis indicates the number of cubic centimeters injected. The second numeral and the letter M give the dilution in terms of millions; e. g., "10(2,4M)" indicates a rise in blood pressure of 10 mm. of mercury after the injection of 2 cc. of a 1 to 4,000,000 solution of epinephrine.

immediate rise of only from 2 to 5 mm., which was interpreted as a doubtful or negative result. Instead of a quick return to the control level, the blood pressure might remain elevated from five to ten minutes or indefinitely. This reaction has been termed "sustained" and was at times definitely attributable to the vasomotor stimulation of respiratory embarrassment following the injection. It was frequently observed, however, apart from dyspnea and was particularly likely to occur when the initial blood pressure was relatively low. This aspect will be discussed later, in connection with the influence of the intravenous injection of saline solution under similar conditions. The different types of reaction of the blood pressure are illustrated in figures 1 and 2.

TABLE 3.—*The Association of Low Blood Pressure in the Rat and the Pressor Effect of Human Plasma* *

				Plasma			
Patient	Age	Diagnosis	Rat	Control Blood Pressure, Mm. Hg	Pressor Effect	Control Blood Pressure, Mm. Hg	Pressor Effect
P. S.	59	AH	46	138	0(1)	62	16(1)
R. S.	26	NH	50	131	8(1,S)	64	19(2)
H. W.	31	MH	51	118	0(1)	62	7(1)
E. B.	51	NH	53	126	0(1)	80	9(1)
K. K.	59	UH	66	122	0(1)	70	9(1)
M. S.	52	HH	103	136	0(2)	76	20(2,S)
E. H.	43	HH	133	142	5(2)	76	24(1.5,S)
H. P.	23	MH	134	132	4(2)	72	16(2)
K. M.	72	HH	125	110	0(2)	96	5(1.S)
G. S.	37	HC	140	128	0(2)	88	9(1)
J. F.	79	MD	155	78	20(2,S)	101	5(1,S)
A. F.	63	HH	158	138	0(1)	87	11(1.2,S)
G. C.	46	NH	164	140	0(1)	105	19(2)
M. S.	58	NH	165	142	0(2)	63	12(2)

* Explanation of the symbols used is given in the footnotes to table 2.

The relation between the effects of human plasma on the blood pressure of the rat and the type of clinical material is summarized in table 1. The details of representative experiments are given in table 2. It is demonstrated that definite pressor effects were obtained with the plasmas of from 35 to 56 per cent of the patients in each of the main clinical groups, whether hypertensive or not. Although the number of persons with "malignant" hypertension and of those without hypertension was rather small, the occurrence of negative effects with two thirds of the plasmas of the former and of positive effects with half of the plasmas of the latter is undoubtedly significant. Analysis of the 23 experiments carried out with plasmas from patients with "malignant" or "pale" hypertension indicates clearly that when positive, or pressor, effects were observed, the rise in blood pressure was not greater than that in animals giving a pressor response to plasmas from patients with "benign" hypertension or without hypertension. Thus, with plasmas

from the group with "malignant" hypertension, the rise in blood pressure varied between 7 and 15 mm., averaging 9.5 mm.; with plasmas from the group without hypertension the rise varied between 5 and 15 mm., averaging 8.2 mm. There was no qualitative difference between the effects of plasmas from patients with "malignant" hypertension and those of plasmas from other patients.

The influence of many variables is possible in experiments of this type. To mention only the more obvious ones, there are the level

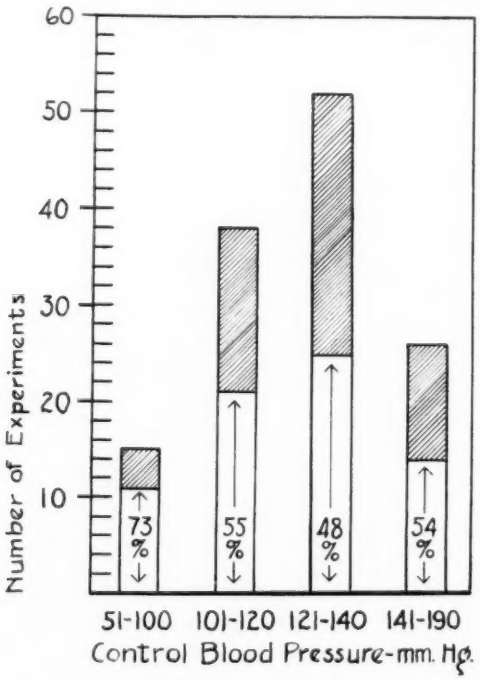


Fig. 3.—The relation between the control blood pressure of the rat and the incidence of pressor effects of heparinized human plasma. The clear rectangles represent positive or pressor effects; the inside figures give the percentage of the total. The shaded rectangles represent negative effects.

of the control blood pressure, the depth of anesthesia, the volume of fluid injected prior to the injection of the plasma under study, the order of injection of various hemodynamic (plasma and epinephrine) and indifferent solutions, the vasomotor reactivity of the rat and the unequal concentrations of pressor substances in human plasma at different times. In order to evaluate the rôle of some of these factors,

the experimental records have been analyzed carefully from several angles.

The level of the rat's blood pressure prior to the initial injection of heparinized plasma seemed to have little effect on the response if it

TABLE 4.—*Results of Repeated Experiments with Plasmas from the Same Patients* *

					Plasma		Saline Solution			
Patient	Age	Diagnosis	Date	Rat	Control Blood Pressure, Mm. Hg	Pressor Effect	Control Blood Pressure, Mm. Hg	Pressor Effect	Anesthesia	Clinical Condition
J. G.	63	HH	3/22/33	20	137	0(1)	...	.....	Deep	
			4/21/33	42	108	0(1)	...	.....	Deep	Unchanged
			6/23/33	69	115	8(1)	111	11(1)	Light	Unchanged
			12/ 1/33	121	122	10(2,S)	132	0(2)	Light	Unchanged
C. W.	50	HH	4/ 3/33	29	110	0(2)	...	.....	Deep	
			6/ 5/33	60	118	13(1)	128	5(2)	Light	Unchanged
R. S.	26	NH	5/ 3/33	50	136	4(1)	...	.....	Deep	General edema
			6/13/33	65	126	12(1)	12[illegible]	7(1,S)	Light	No edema
E. B.	51	NH	5/18/33	53	126	9(1)	...	. ....	Deep	Acute colitis
			10/ 2/33	85	140	6(1,S)	148	0(1)	Light	Acute heart failure
			10/ 3/33	86	142	8(1,S)	141	11(1,S)	Light	Unchanged
			1/11/34	135	146	10(2)	142	0(2)	Light	Chronic heart failure
C. E.	46	MH	5/25/33	57	114	9(1)	104	0(1)	Deep	
			5/31/33	58	84	12(1,S)	...	.....	Light	Unchanged
K. B.	39	UH	6/28/33	72	126	10(1,S)	107	5(1)	Light	
			9/26/33	84	154	6(1,S)	156	7(1,S)	Light	Unchanged
E. A.	50	HH	9/15/33	78	114	10(1,S)	...	.....	Light	
			10/12/33	92	122	20(2,S)	114	12(1,S)	Light	Unchanged
			2/16/34	150	134	0(2)	...	.....	Light	Unchanged
			11/ 6/34	163	154	7(1)	148	0(1)	Light	Unchanged
E. H.	43	HH	11/ 7/33	107	136	7(2)	125	10(1,S)	Light	Early heart failure
			1/ 9/34	133	142	5(2)	136	14(2,S)	Light	Coronary occlusion
			1/31/34	143	128	6(2)	124	0(2)	Light	Severe heart failure
W. M.	25	HH	11/10/33	110	120	12(2,S)	...	.....	Light	
			11/17/33	114	123	0(2)	125	11(1)	Light	Unchanged
H. P.	23	MH	11/24/33	117	104	15(2,S)	104	12(2)	Light	Uremia; acute neuroretinitis
			12/ 4/33	122	120	8(2,S)	116	7(2)	Light	Unchanged
			1/10/34	134	132	4(2)	...	.....	Deep	Acute heart failure
A. S.	50	HC	1/30/34	142	131	15(2,S)	128	0(2)	Light	
			2/ 1/34	144	128	14(2)	135	8(2)	Light	Unchanged
J. H.	41	MD	10/29/34	159	131	0(1)	131	0(1)	Light	
			10/30/34	160	156	7(2)	156	0(1)	Light	Unchanged
I. W.	21	HC	10/30/34	160	156	8(2)	156	0(1)	Light	
			10/31/34	161	138	6(2)	120	0(1)	Deep	Unchanged

* Explanation of the symbols is given in the footnotes to table 2.

lay above 100 mm. of mercury, which was the case in 89 per cent of the experiments. However, in rats with a blood pressure of 100 mm. or less, there was a higher incidence of positive, or pressor, effects, as shown in figure 3. If the significance of this difference could be

doubted because of the small number of experiments, confirmatory evidence was found in the experiments in which, for one reason or another, the rat's blood pressure dropped from a normal level to a considerably lower one. In 17 rats which had given little or no response to plasma injected at the normal level of blood pressure, pressor effects were obtained with injections at the hypotensive level. Details are given in table 3. The fact that with either initial or late hypotension the pressor effect of injected plasma was likely to be sustained suggested a beneficial increase in the circulating blood volume as the direct cause of the positive result.

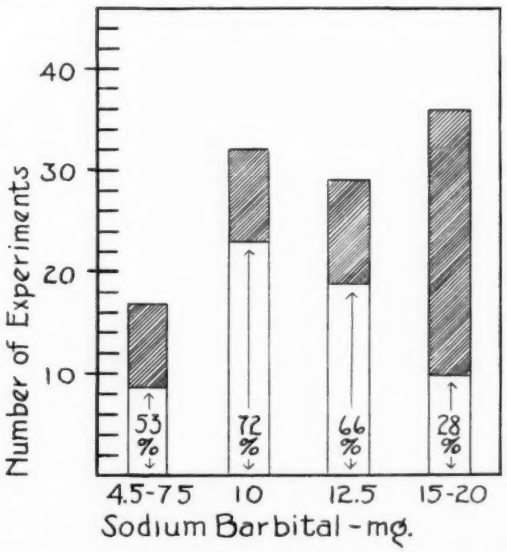


Fig. 4.—The relation between the amount of anesthetic (sodium barbital) and the pressor effect of heparinized plasma in the rat. The clear rectangles represent positive or pressor effects; the inside figures give the percentage of the total. The shaded rectangles represent negative plasmas.

The rôle of anesthesia is indicated in figure 4. When the amount of sodium barbital exceeded 15 mg., the number of experiments without pressor effects from plasma was about three times the number of experiments showing pressor responses. In contrast, the negative results were only half as numerous as the positive results when the dosage of sodium barbital was between 5 and 15 mg. Variation in the amount of anesthetic used may well have been a factor in the dissimilar response of different rats to samples of plasma from the same patient. This is illustrated in table 4.

The volume of fluid given intravenously prior to the first injection of heparinized plasma might be considered as a factor in the rat's response to plasma, because of the small blood volume of the animal and the possible change in the depth of anesthesia and vasomotor reactivity during a number of five to fifteen minute intervals between injections. Of 69 rats into which plasma was injected first, only 20 showed a pressor effect, while 22 of 35 rats given 2 cc. of saline solution or solution of epinephrine prior to the first injection of plasma gave a pressor response to the latter. This would seem to indicate that a moderate increase in the rat's blood volume may be a helpful factor in the pressor response to plasma. That this is not entirely true is shown by the regular decrease in response to successive administrations of plasma after the first pressor effect and by the failure of the second or third injection of plasma to produce an elevation in blood pressure if the first dose had no effect. Furthermore, the 69 rats given plasma on the first injection happened to include 29 rats which had received more than 15 mg. of sodium barbital, or 85 per cent of the rats with the deepest anesthesia. This circumstance, as discussed in the preceding paragraph, would of itself tend to reduce the number of positive, or pressor, results in this series.

The order of injection of hemodynamic solutions, such as plasma, epinephrine or plasma plus epinephrine, was varied in different experiments. Of 6 rats given epinephrine in saline solution prior to the first injection of plasma, 4 showed no response to plasma and 2 had a rise of only 5 mm. All of them had reacted well to epinephrine. In 15 other rats, epinephrine in saline solution or plasma plus epinephrine or both were injected after the first dose of plasma. After the usual interval, another injection of plasma was given. In none of these experiments was the reaction to the postepinephrine injection of plasma greater than the response to the first, or preepinephrine, injection of plasma. In other words, there was no evidence that the previous intravenous administration of epinephrine in an amount sufficient to produce a typical rise in blood pressure heightened the vasomotor reactivity of the rat to heparinized human plasma. Furthermore, in 24 rats the rise in blood pressure produced by a given dose of epinephrine, usually 0.0005 mg., in physiologic solution of sodium chloride, was compared with the pressor effect of the same amount of epinephrine in heparinized plasma. Other variables were carefully controlled. The average rises in blood pressure were 12.4 and 13.6 mm., respectively. Epinephrine in plasma tended to give slightly more prolonged pressor effects than epinephrine in physiologic solution of sodium chloride. Eleven of the 24 rats received injections of plasmas which caused pressor activity. Hence, the group was a fair sample of the entire series. From these results there was no evidence of a synergistic action

in the rat between the plasmas from hypertensive patients and the minimal effective doses of epinephrine.

The vasomotor reactivity of the rat was tested in two ways, by means of epinephrine and by the injection of physiologic solution of sodium chloride. The injection of epinephrine was carried out in 98 of the 131 rats. The minimal effective dose corresponded to about 0.0008 mg. per kilogram of body weight per minute, when injected at the rate of 1 cc. per minute of a 1 : 4,000,000 solution in physiologic solution of sodium chloride, freshly prepared by diluting the commercial 1 : 1,000 solution. A definite depressor effect was never observed. Epinephrine, in contrast to saline solution or plasma, never caused a sustained rise in blood pressure at the ordinary levels.

The control injection of physiologic solution of sodium chloride, in amounts of 1 or 2 cc., was performed in 77 rats. The control levels of blood pressure after the injections lay at 101 mm. of mercury or above in 91 per cent of the experiments, as was true following the injections of plasma. A rise in blood pressure occurred in 42 rats, but in only 9 of these was there no effect from heparinized plasma. The coincidence of such factors as jerking of the lightly anesthetized animals, failure of the blood pressure to return to the control level after the injection ("sustained" rise) and difficulty in the interpretation of the graphic record for 8 of the 9 rats should eliminate this group from serious consideration as an exception to the general result that rats responded with a pressor effect to plasma whenever they reacted positively to the more temporary increase in blood volume produced by saline solution. In 13 rats the blood pressure was unaffected by either plasma or saline solution. Of the 31 rats that gave pressor response to both plasma and saline solution, the records for 25 were satisfactory for further analysis. Here again, about 90 per cent of the control levels of blood pressure were above 100 mm. of mercury, and 40 per cent lay between 121 and 140 mm. Simple averaging of the rises in blood pressure produced by the injection of 0.9 per cent saline solution or plasma resulted in an identical figure for both, 11 mm. However, careful study of the records of the individual experiments revealed that saline solution was injected first in 19 of the 25 rats; that the rise was "sustained" in 13 of the 19 animals but in only 1 of the remaining 6; that plasma produced a "sustained" rise in only 6 of the 13 experiments in which there was a "sustained" response as the initial effect of the saline solution, and that the pressor effect of saline solution exceeded the pressor effect of plasma in only 2 of the 25 animals if the two factors just mentioned were taken into account, while the pressor effect of plasma surpassed the pressor effect of saline solution in 11 experiments, including 8 in which saline solution was injected first. From these

results it was apparent that the "control" injection of saline solution was not a true control if given at the very beginning of the experiment because it tended to produce an exaggerated rise of blood pressure, which, since it was "sustained" in two thirds of the animals, strongly suggested an increase of a temporarily diminished circulating blood volume as the cause of the observed pressor effect. The conclusion was strengthened by the occurrence of pressor effects of plasma at low levels of blood pressure (below 100 mm. of mercury) in all of 11 rats tested which had previously given no response to plasma at higher or normal levels of blood pressure (table 3). In 5 of these rats the pressor effect at the hypotensive level was "sustained." A characteristic feature of the "sustained" effect, whether produced by saline solution or by plasma, was the magnitude of the rise, usually from 10 to 20 mm.

The analysis of 17 experiments in which heparinized plasma gave a pressor effect while saline solution produced no change in the blood pressure revealed that in 4 rats the plasma was injected first; however, the rise was "sustained" in only 1 of these. Of the other 13 rats, 5 gave a "sustained" response to plasma injected in amounts of 2 cc. The clinical material represented in this series of 17 experiments included 8 cases of "benign" hypertension and its sequels, 2 cases each of "malignant" hypertension and glomerulonephritic hypertension, 1 case of arteriosclerotic hypertension and 4 of nonhypertensive conditions. In other words, there was nothing remarkable about the clinical sources of the samples of plasma.

Possible variations in the concentration of the pressor substances in the plasma of a given patient at different periods were investigated by means of repeated experiments with plasma from 22 patients (table 4). The interval between the taking of samples varied from twenty-four hours to one year. In 11 cases the results were constant, and in 6 of the remaining 11 there were sufficient differences in the depth of anesthesia or in the control levels of the blood pressure of the rat to account for observed inconsistencies. Marked changes in the patient's clinical condition seemed to have much less influence on the experimental result than the state of the various rats used. On the whole, plasma from a given patient tended to produce constant effects. However, a much larger series of multiple experiments would be necessary to allow a definite conclusion on this point.

COMMENT

The search for a chemical pressor substance in the blood of hypertensive patients is not new. Janeway in 1913 [2] reviewed the earlier experiments critically and discarded the hypothesis that epinephrine was responsible for clinical hypertension. As to pressor effects in

general, the experiments of Stewart [7] gave negative results, but the amount of human serum injected into dogs was undoubtedly too low. Danzer, Brody and Miles [8] reported positive or pressor results with whole blood injected into cats. The somewhat similar experiments of Curtis, Moncrieff and Wright [9] led to the opposite conclusion. Høst [10] performed many transfusions of blood from hypertonic subjects to patients with normal blood pressure without observing any significant effects on the blood pressure of the latter.

It required the work of Bohn [4a] to give a new impetus to the search for pressor substances in the blood of hypertensive subjects. In 1931 he reported that alcoholic extracts of whole blood from 100 normal persons and 84 patients with "red" hypertension caused a 10 to 20 mm. fall in the blood pressure of curarized cats which had received ethyl carbamate (urethane). On the other hand, similar extracts of blood from 19 patients with "pale" hypertension ("malignant" nephrosclerosis) produced a rise in blood pressure of from 10 to 20 mm. when injected intravenously into cats. There were admittedly difficulties in these experiments, since depressor effects occurred in one test or another in half of the patients with "pale" hypertension. Pressor effects were also obtained with extracts of plasma from 10 patients with "transitional" (i. e., from "red" to "pale") hypertension, from 7 of 10 patients with acute diffuse glomerulonephritis and from a number of patients with chronic hypertensive glomerulonephritis and uremia. In general, therefore, these results corroborated Volhard's [5] theoretical speculations on the etiology of clinical hypertension.

Repetition of Bohn's work by other investigators has led to conflicting results. Marx and Hefke [11] reported prolonged rises in the blood pressure of from 15 to 45 mm. of mercury in trained unanesthetized dogs into which were injected alcoholic extracts of from 80 to 100 cc. of blood from patients with "malignant" hypertension. The maximum response occurred with extracts of blood from patients with acute nephritis or contracted kidneys. Unfortunately, similar results were also obtained with extracts of blood from epileptic patients.

---

7. Stewart, G. N.: So-Called Biological Tests for Adrenalin in the Blood, with Some Observations on Arterial Hypertonus, J. Exper. Med. **14**:377, 1911.

8. Danzer, C. S.; Brody, J. G., and Miles, A. L.: Existence of Pressor Substance in Blood of Clinical Case of Hypertension, Proc. Soc. Exper. Biol. & Med. **23**:454, 1926.

9. Curtis, F. R.; Moncrieff, A. A., and Wright, S.: Supposed Presence of Pressor Substance in Blood of Patients with High Blood Pressure, J. Path. & Bact. **30**:5, 1927.

10. Høst, H. F.: Experimental Investigations of Hypertonia, Acta med. Scandinav. **77**:28, 1931.

11. Marx, H., and Hefke, K.: Untersuchungen zur Pathogenese der Hypertonie, Klin. Wchnschr. **12**:1318, 1933.

There was no direct correlation between the height of the patient's blood pressure and the amount of pressor effect. A carefully conducted series of experiments by de Wesselow and Griffiths,[12] in which various methods of extraction were used, led the authors to conclude that the first effect of all extracts of whole blood was a rapid fall in the blood pressure of cats; that the pressor effects of extracts of whole blood were the same for normal persons and for donors with "malignant" hypertension and scarcely differed from the slight rise following the injection of 5 cc. of Tyrode's solution, and that extracts of whole blood from patients with "benign" hypertension gave the most marked pressor results. However, extracts of the plasma had no effects in the last group and, in general, were physiologically identical in the normal persons and in those with a pathologic condition. Ultrafiltrates of human plasma never showed pressor effects. In short, Bohn's conclusions were entirely contradicted, both as to fact and as to theory.

In a more recent publication, however, Bohn and Schlapp [4b] described an improved method for extracting human plasma to get rid of depressor substances and laid down strict conditions for the rest of the experimental procedure in order to control the depth of anesthesia, the initial level of the cat's blood pressure, the number and nature of solutions injected and other variables. Strongly pressor effects were again reported from plasma of patients with "malignant" hypertension and chronic nephritis, but early depressor, with later pressor, effects were present in the plasma of patients with acute nephritis, before eclampsia and during eclampsia. Contrasting with these results are the thorough studies of Page [13] and of Capps, Ferris, Taylor and Weiss.[14] Page has detected a powerful pressor substance in extracts of the plasma and other body fluids of human subjects without observing an increased amount in the plasma of patients with various types of hypertension. Capps and his associates have worked with acetone and alcohol fractions of both the blood and the urine of normal and hypertensive persons. The extracts of blood produced no significant pressor effect, regardless of the clinical source. The urinary extracts usually contained pressor material, but there was no significant difference between the normal and the hypertensive subject in respect to the quantity of pressor substance excreted. Elliott and Nuzum,[15] who injected citrated human

12. de Wesselow, O. L. V. S., and Griffiths, W. J.: On the Question of Pressor Bodies in the Blood of Hypertensive Subjects, Brit. J. Exper. Path. **15**:45, 1934.

13. Page, I. H.: The Nature and Action of a Pressor Substance Found in Body Fluids of Man, J. Clin. Investigation **13**:703, 1934.

14. Capps, R. B.: Ferris, E. B.; Taylor, F. H. L., and Weiss, Soma: Rôle of Pressor Substances in Etiology of Arterial Hypertension, Proc. Soc. Exper. Biol. & Med. **31**:1106, 1934.

15. Elliott, A. H., and Nuzum, F. R.: Possibility of Pressor Principle in Blood of Persons with Hypertension: Experimental Study, J. Lab. & Clin. Med. **18**:1255, 1933.

blood into rabbits, also failed to observe striking differences in vasomotor effects between blood from normal and that from hypertensive persons.

The present study has been in progress since 1932. At first, 12 trained unanesthetized dogs were used. Their blood pressure was recorded directly from the transplanted common carotid or femoral artery, according to the method of Dragstedt.[16] Heparinized plasma of human blood was injected intravenously in amounts varying from 4 to 20 cc. The samples of blood came from 31 patients with various types of hypertension, including 7 in the "malignant" stage. Plasma from 16 nonhypertensive patients was also tested. The results were entirely negative in all but 4 instances and in only 1 of these was plasma used from a patient with "malignant" hypertension. Repeated experiments were carried out with the plasma of 3 patients with "malignant" hypertension. The factor of dilution of the patient's blood by the dog's blood volume was naturally considered as the most likely explanation for the absence of pressor effects. Hence, the rat was chosen as the experimental animal for the remainder of the work. Incidentally, it was possible to confirm Dragstedt's[16] observations in regard to the minimal effective dose of epinephrine and the absence of a depressor response in the unanesthetized dog.

The results of the injection of heparinized human plasma into rats have already been discussed in some detail. Critical consideration of the experimental procedure reveals serious drawbacks, e. g., the small blood volume of the rat and the danger of overloading the circulatory system by even a few injections, the possible delayed toxic effect of foreign protein, the difficulty of controlling the degree of anesthesia and respirtory ventilation and the absence in all but the last 12 experiments of comparative observations on injections of different plasmas in the same rat. However, in spite of these and other difficulties, there is no doubt that the pressor effect in the rat of plasma from a patient with "malignant" or "pale" hypertension is indistinguishable from the pressor effect of plasma from a patient with a nonhypertensive condition or "benign" hypertension. Furthermore, the percentage of positive results was about the same for all clinical groups (table 1). That the positive or pressor response must be interpreted in relation to the animal's circulating blood volume, level of blood pressure and depth of anesthesia has already been demonstrated. The previous injection of epinephrine seems to have little bearing on the later response of the rat to human plasma. It is important, however, to rule out volume effects on the blood pressure by preliminary injections of saline or other solutions until the

16. Dragstedt, C. A.: Observations on Hemodynamic Action of Epinephrine, J. A. M. A. **91**:1033 (Oct. 6) 1928.

blood pressure is stabilized. This undoubtedly applies to other animals as well as to the rat, especially when a general anesthetic is employed and the experiment is prolonged.

The pressor effect in the rat of heparinized human plasma is not dramatic. In terms of epinephrine it would correspond usually to a minimal effective dose. Of course, the material injected has been diluted from ten to thirty times by the rat's own blood. Judging from the extreme rarity of immediate depressor effects, human plasma is not toxic to the rat. In fact, in a number of animals in which the blood pressure had dropped to low levels during the course of an experiment, the repeated injection of plasma or packed red corpuscles from human blood or mixtures of the two has resulted in a return of the blood pressure to a normal level and marked improvement in the general condition of the rat.

The nature of the pressor substance apparently present in many human plasmas has not been investigated in this study. Chemical treatment of the plasma was purposely avoided. Ultrafiltration was not attempted because of the uniformly negative results reported by other investigators. The difference between temporary and "sustained" pressor responses could not be traced to any known difference in the clinical source of the material. Plasma mixed with epinephrine usually produced no greater or less rise in the blood pressure than the control reaction to epinephrine in saline solution. Therefore, the pressor material in human plasma is not a sensitizer to epinephrine in the rat.

Whether the pressor activity is a constant or variable feature of the plasma of certain persons with or without hypertension has not been definitely established in this work. It is possible that repeated testing with plasma which originally caused a negative effect might yield positive results in some experiments. The interpretation of such variations is rather subjective, because of the difficulty in controlling conditions in the experimental animal. The old advice of Stewart [7] to "fractionate" the test object or the material tested is very timely.

One may conclude from the experiments reported here that no evidence has been obtained to support the views of the Volhard group that the etiology of "pale" hypertension is intimately related to a pressor substance in the circulating blood of the diseased person. On the contrary, an apparently identical pressor effect is produced by plasma from patients with "benign" hypertension or with normal blood pressure. Whether the pressor action of heparinized plasma in the rat is caused by the same material which other investigators have studied in various extracts of whole blood, plasma, urine or other body fluids has not been determined; but it is reasonable to assume that a common agent is involved in all these experiments. The more important question of the

rôle of such pressor substances in human cardiovascular physiology cannot be answered at present without unjustifiable speculation.

SUMMARY

In preliminary experiments the intravenous injection of heparinized plasma of human blood into unanesthetized dogs produced no significant changes in the mean blood pressure, directly recorded. No difference was observed between the effects of plasma from nonhypertensive persons and the effects of plasma from "malignant" hypertensive patients.

The use of the rat as the test animal, to diminish the dilution of the injected plasma by the animal's blood volume, made possible the demonstration of pressor effects from 51, or 44 per cent, of 117 heparinized plasmas.

The distribution of pressor effects of the plasmas among the different clinical groups was independent of the type of hypertension or of the presence of hypertension.

Plasmas from 17 patients with "malignant" hypertension gave no higher incidence of pressor effects or greater rises in blood pressure than plasmas from 100 other subjects, of whom 83 had various types of hypertension and 17 had miscellaneous nonhypertensive conditions.

Plasmas from hypertensive patients did not increase the response of the blood pressure of the rat to minimal effective doses of epinephrine.

As a result of this study and the related work of other investigators, it must be concluded that there is no satisfactory evidence for the theory that "malignant" or "pale" hypertension (or, for that matter, any common form of clinical hypertension) is caused by the presence of pressor substances in the patient's blood.

RELATIVE VALUES OF CAFFEINE AND HYPERTONIC DEXTROSE AND SALINE SOLUTIONS IN REDUCING CEREBROSPINAL FLUID PRESSURE

ABRAM BLAU, M.D.
NEW YORK

The intravenous injection of a hypertonic solution of dextrose for the purpose of reducing the cerebrospinal fluid pressure is a common procedure in the treatment of neurologic disturbances, although few direct observations of its effects have been reported in the literature. The procedure is based mainly on a number of experimental studies on animals.[1]

During exploratory craniotomy, Fay[2] observed a decrease in the dural tension following the intravenous administration of a 15 per cent saline solution. A number of observers have measured the effect of these solutions by the application of a tambour next to postoperative cranial defects or herniations, but their results are contradictory. Ebaugh and Stevenson[3] noted a prolonged fall in pressure after the

From the Neurological Service of Dr. Israel Strauss at the Mount Sinai Hospital.

1. (*a*) Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**:512 (May) 1919; (*b*) Experimental Alterations in Brain Bulk, ibid. **48**:531 (May) 1919. (*c*) Weed, L. H., and Hughson, W.: Systemic Effects of the Intravenous Injection of Solutions of Various Concentrations, with Especial Reference to the Cerebrospinal Fluid Pressure, ibid. **58**:53 (Nov.) 1921; Spinal Fluid Pressure in Relation to the Bony Encasement of the Central Nervous System as a Rigid Container, ibid. **58**:85 (Nov.) 1921; Intracranial Venous Pressure and Spinal Fluid Pressure as Affected by Intravenous Injection of Solutions of Various Concentrations, ibid. **58**:101 (Nov.) 1921. (*d*) Sachs, E., and Malone, J. Y.: The Use of Hypertonic Salt in Experimentally Increased Intracranial Pressure, ibid. **55**:277, 1921. (*e*) Howe, H. S.: Experimental Studies in the Reduction of the Normal Cerebrospinal Fluid Pressure in Cats, A. Research Nerv. & Ment. Dis., Proc. **4**:220, 1926. (*f*) Milles, G., and Hurwitz, P.: Effect of Hypertonic Solutions in Cerebrospinal Fluid Pressure with Special Reference to Secondary Rise and Toxicity, Arch. Surg. **24**:591 (April) 1932. (*g*) Ernst, Max: Untersuchungen über die Wirkung anisotonischer Lösungen auf Gehirn und Liquor, Deutsche Ztschr. f. Chir. **226**:222, 1930.

2. Fay, T.: The Administration of Hypertonic Salt Solutions for the Relief of Intracranial Pressure, J. A. M. A. **80**:1445 (May 19) 1923.

3. Ebaugh, F. G., and Stevenson, G. S.: Measurements of Intracranial Pressure Changes in an Epileptic and Its Experimental Variations, Bull. Johns Hopkins Hosp. **31**:440 (Dec.) 1920.

intravenous administration of 200 cc. of a 30 per cent dextrose solution, while Stevenson and his associates [4] noted only a slight effect. Foley [5] used a 15 per cent saline solution and observed a definite decrease of the herniation. The more direct method of continuously measuring the spinal fluid pressure by means of lumbar puncture and a manometer has been applied more recently. With this technic, Foley [5] noted a marked fall with the administration of 190 cc. of a 15 per cent saline solution, Browder [6] noted both a moderate fall and a distinct rise with 100 cc. of a 50 per cent dextrose solution, and Haug [7] reported only a slight indefinite change caused by either solution. Milles and Hurwitz,[1f] Jackson and his co-workers [8] and Masserman [9] observed a primary transient rise, a secondary reduction and, finally, a tertiary rise above the normal a short time (from one-half to three hours) after the intravenous injection of up to 200 cc. of dextrose solution. By a similar technic Denker [10] and Haug [7] demonstrated a constant decrease of the cerebrospinal fluid pressure for about one half hour following the intravenous injection of caffeine.

Since the common procedure in the clinical use of dextrose is to inject about 50 cc. of a 50 per cent solution, more or less rapidly, intravenously with a syringe, and since saline solutions have not been sufficiently employed, the problem appeared to require further investigation. Furthermore, no observations have been reported in patients with increased intracranial pressure. The purpose of this report is to record the results of a study of the effect on a number of persons with normal and abnormal cerebrospinal fluid pressure when hypertonic solutions of dextrose and sodium chloride and of caffeine were administered intravenously in a short period of time.

---

4. Stevenson, L.; Christensen, B., and Wortis, S. B.: Some Experiments in Intracranial Pressure in Man During Sleep, Am. J. M. Sc. **178**:663 (Nov.) 1929.

5. Foley, F. D. B.: Clinical Uses of Salt Solutions in Conditions with Increased Intracranial Tension, Surg., Gynec. & Obst. **33**:126 (Aug.) 1921.

6. Browder, J.: Dangers in the Use of Hypertonic Solutions in the Treatment of Brain Injuries, Am. J. Surg. **8**:1213 (June) 1930.

7. Haug, K.: Klinische und pharmakodynamische Untersuchungen des Liquordrucks vermittelst Dauerdruckmessungen bei Geisteskranken, Arch. f. Psychiat. **97**:189, 1932.

8. Jackson, H.; Kutsunai, T.; Leader, L. O., and Joseph, L. D.: Effects of Hypertonic Dextrose Solutions in Intracranial Pressure, J. A. M. A. **100**:731 (March 11) 1933.

9. Masserman, J. H.: Effects of Intravenous Administration of Hypertonic Solutions of Dextrose, J. A. M. A. **102**:2084 (June 23) 1934.

10. Denker, P. G.: The Effect of Caffein on the Cerebrospinal Fluid Pressure, Am. J. M. Sc. **181**:675 (May) 1931.

METHOD

The study was carried out during routine tests by lumbar puncture on patients from the neurologic service of Dr. Israel Strauss. The patients were chosen according to their ability to remain in the lateral position on the right side for the period required. The ages of the patients studied varied from 9 to 68 years. No sedative was administered, but as a reassuring preliminary measure the procedure was explained to the patient as much as possible. With local anesthesia, a lumbar puncture was made in the third lumbar space, and a glass manometer was attached with the loss of only 2 or 3 drops of fluid. A Queckenstedt test was performed to insure the patency of the system. Readings were then made until the basic normal variations were established, usually for from fifteen to thirty minutes. After this, the solution was injected into the median basilic vein with a large syringe, and the readings were continued at one minute (or more frequent) intervals for a varying period, as conditioned by the patient's cooperation. Before the termination of the examination the Queckenstedt test was repeated. The observation was discarded if the patient proved uncooperative, if the needle did not enter the subarachnoid space without mishap, if more than 2 or 3 drops of fluid was lost or if the cerebrospinal fluid system did not remain freely patent, as shown by the cardiac and respiratory oscillations and the Queckenstedt test. A total of fifty-one observations are reported (in some instances the same patient was used for more than one): fifteen with 50 cc. of a 50 per cent dextrose solution, thirteen with 100 cc. of a 50 per cent dextrose solution, seven with 50 cc. of a 15 per cent saline solution, eight with 100 cc. of a 15 per cent saline solution and eight with 5 grains (0.3 Gm.) of caffeine sodium benzoate. The last group confirmed the findings of other workers and served as a control.

OBSERVATIONS AND COMMENT

These observations are completely presented in charts 1 to 5. The ordinate unit represents 20 mm. of cerebrospinal fluid pressure, and the abscissal unit, two minutes of time each. The perpendicular line preceding each reading denotes the preliminary variation of pressure taken as the basic standard. It is interesting that the extent of normal variations in the individual cases varied somewhat directly with the height of the pressure and was most marked in the cases of tumor of the brain. A significant fact is that in the cases of tumor of the brain there were wide rapid oscillations, even more striking than can be shown in a graph on such a small scale; this was most marked in the cases of the neoplasm of the posterior fossa (cases 25 and 50).

In most cases there was a rise in pressure preceding the injection; this was due to the application of the tourniquet. A primary rise in pressure following the injection was not a constant observation as reported by others.[11]

Chart 1 demonstrates the result of the administration of 50 cc. of a 50 per cent solution of dextrose. The average duration of the injec-

11. Milles and Hurwitz.[1f] Jackson, Kutsunai, Leader and Joseph.[8] Masserman.[9]

tion was one minute and thirty-eight seconds. In only two cases (1 and 9) was there a slight lowering of the pressure; in ten cases, including one of tumor of the brain (2, 3, 4, 5, 10, 11, 12, 13, 14 and 15),

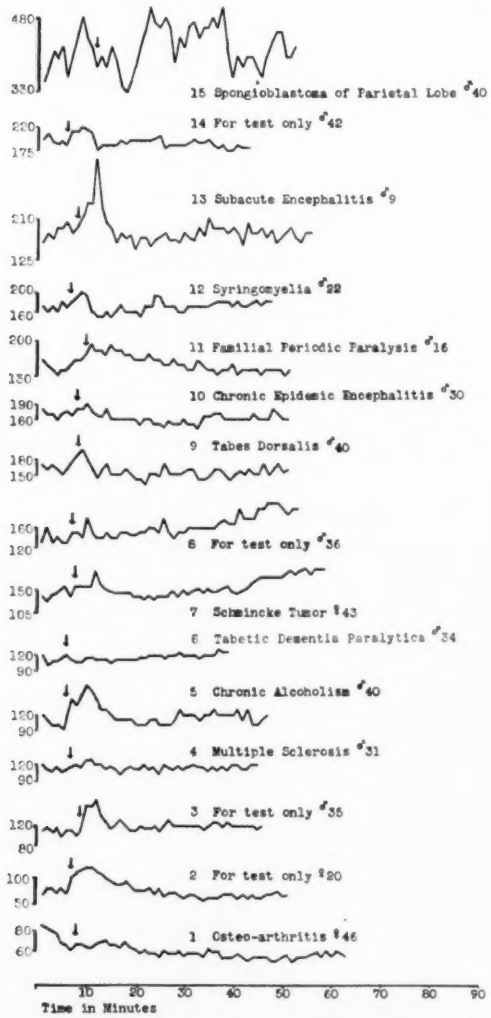


Fig. 1 (cases 1 to 15).—The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 50 cc. of a 50 per cent solution of dextrose.

there was no significant change, while in three cases (6, 7 and 8) there was a definite rise. The injections of 100 cc. of hypertonic solution of dextrose averaged two minutes and ten seconds each, and the obser-

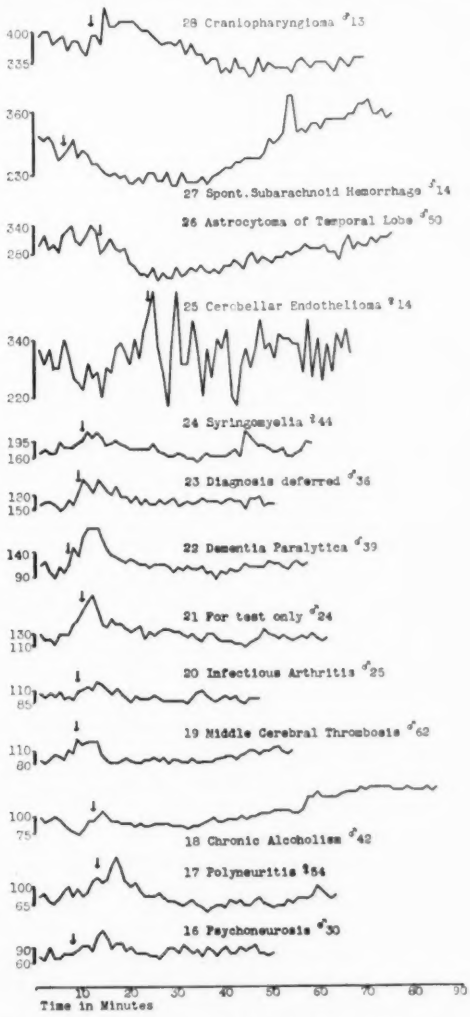


Fig. 2 (cases 16 to 28).—The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 100 cc. of a 50 per cent solution of dextrose.

vations are shown in chart 2. A temporary fall occurred in only five cases (17, 24, 26, 27 and 28), three being cases of increased intracranial pressure. In seven cases, including one of tumor of the brain (16, 19, 20, 21, 22, 23 and 25), there was no appreciable effect, while in one case (18) there was a definite marked rise above the normal pressure.

The injection of hypertonic saline solution caused a definite decrease in the cerebrospinal fluid pressure in all the cases (charts 3 and 4).

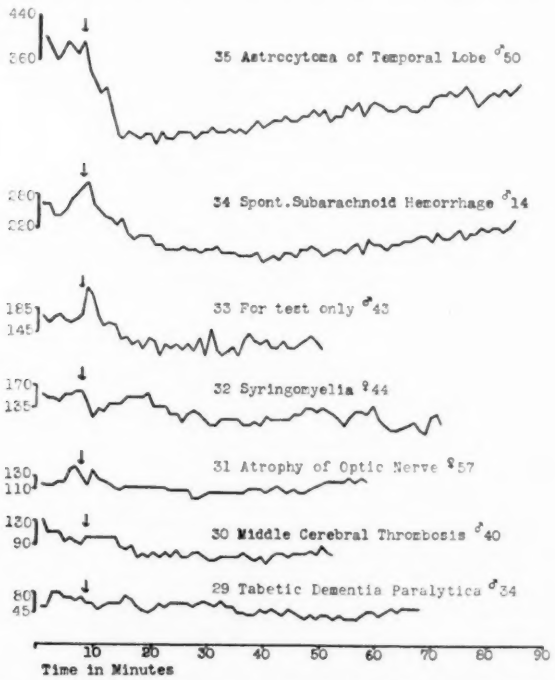


Fig. 3 (cases 29 to 35).—The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 50 cc. of a 15 per cent solution of sodium chloride.

The average duration of the two doses was, respectively, two minutes, forty seconds and six minutes, forty seconds. With the doses of 50 cc. the effect was temporary and was comparable to that noted in five cases in which 100 cc. of hypertonic dextrose solution was injected, but a fall in pressure was constant. The reduction was also most marked in the cases of higher intracranial pressure. With 100 cc. of a 15 per

cent saline solution a decrease of the cerebrospinal fluid pressure was observed in all cases, was the most marked in the series and persisted for the full length of the experiment.

The depressant effect of caffeine on the cerebrospinal fluid pressure was confirmed (chart 5), but its duration was transient.

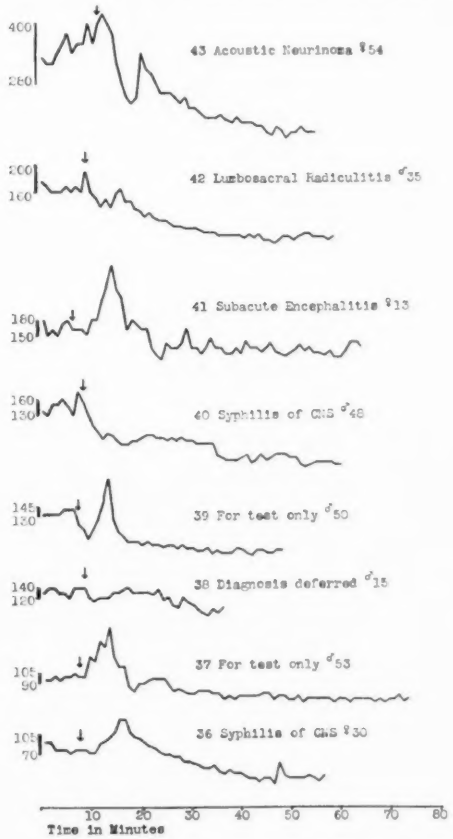


Fig. 4 (cases 36 to 43).—The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 100 cc. of a 15 per cent solution of sodium chloride.

An incidental observation was that when the pressure is decreased by any of the solutions the extent of the fluctuating variations is diminished and the pressure becomes more stable; when there is a return to the original pressure the full extent of the fluctuations recur.

The most important fact in this study is that it demonstrates the superiority of a hypertonic solution of sodium chloride over that of a hypertonic solution of dextrose or caffeine as a depressant of the cerebrospinal fluid pressure. This is in agreement with the original observations of Weed and McKibben [1a] in animals; the solutions of

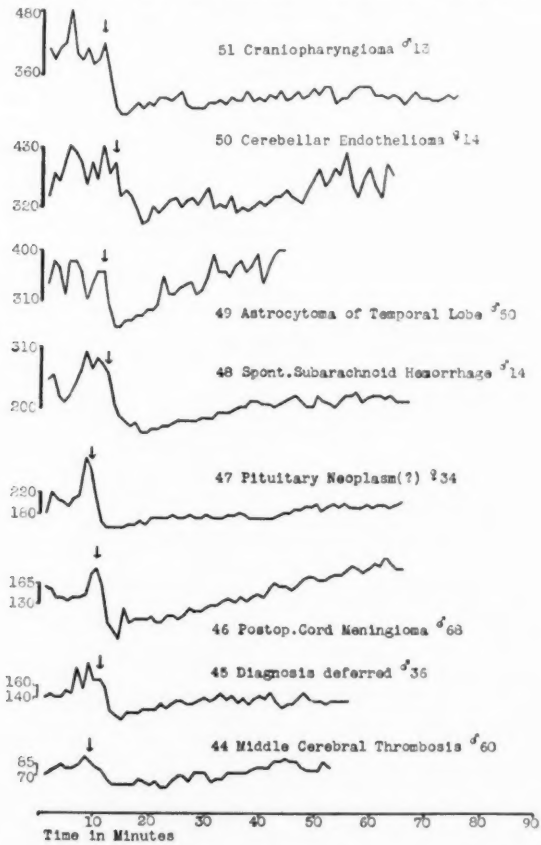


Fig. 5 (cases 44 to 51).—The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 5 grains of caffeine sodium benzoate.

dextrose caused a much smaller effect than did those of the electrolytes. This can be readily accounted for by the fact that the diffusion time of dextrose is three times that of sodium chloride and therefore its osmotic pressure is proportionately less.

It would seem that the saline solutions should displace the dextrose solutions in the clinical application of hypertonic solutions intravenously for the reduction of intracranial pressure. The dextrose solutions offer only slight beneficial effects and may be followed by an aggravation of the condition owing to the subsequent rise in pressure.[11] The toxic effect of hypertonic saline solution is doubtful. In none of the cases was a deleterious effect shown clinically, except for a transient flushing and a complaint of thirst. In two cases the injection was followed by a slight chill, but this was probably due to some pyrogenic impurity in the water.[12] In the treatment of thrombo-angiitis obliterans with repeated injections of hypertonic (5 per cent) saline solution, Silbert[13] has not observed a fatality or a serious reaction in about twenty thousand such injections. The occasional report of adverse results must be attributed to the secondary rise in the cerebrospinal fluid pressure and should be applicable to any of the hypertonic solutions.

SUMMARY

The effects on the cerebrospinal fluid pressure of the intravenous administration of hypertonic dextrose (50 per cent) and saline (15 per cent) solution and a solution of caffeine sodium benzoate (5 grains) were compared in fifty-one observations on normal persons and on patients with increased intracranial pressure. The injection of dextrose solutions was effective in reducing the cerebrospinal fluid pressure in only relatively few cases. In a few cases the injection of a dextrose solution caused an immediate prolonged rise in the pressure. The effect of caffeine was greater and was consistent, but with both the latter and the dextrose the results were transient. The injection of hypertonic saline solution, however, resulted uniformly in a definite and more persistent reduction in the cerebrospinal fluid pressure. It is therefore suggested that hypertonic solutions of sodium chloride should replace the solutions of dextrose in clinical administration for the reduction of intracranial pressure.

12. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, Am. J. Physiol. **67:**90 (Dec.) 1923.

13. Silbert, S.: Thrombo-Angiitis Obliterans (Buerger): V. Results of Treatment with Repeated Injections of Hypertonic Salt Solution, J. A. M. A. **94:** 1730 (May 31) 1930.

LYMPHOBLASTOMA CUTIS

REPORT OF A CASE WITH AUTOPSY

ARTHUR S. ROSENFELD, M.D.
Assistant Professor Clinical Medicine, University of Oregon Medical School
AND
J. V. STRAUMFJORD, M.D.
Pathologist, Dr. R. C. Coffey Clinic and Hospital
PORTLAND, ORE.

The generic name lymphoblastoma cutis, suggested first by Mallory, in 1914, and later by Keim,[1] in 1924, covers a group of dyscrasias of the skin, glands and blood which blend one into the other and are of such rarity and interest as to warrant reporting them. In this group are included Hodgkin's disease, lymphosarcoma, leukemia and mycosis fungoides. Goeckerman stated that there is a growing tendency in this country to regard them as varying clinical manifestations of the same disease. At least, his experience at the Mayo Clinic supported the conception that the diseases are genetically closely related. In some cases a condition with characteristics of one disease has later changed and developed characteristics of another or possibly of several others of the group. Occasional mention of such metamorphoses has been made in the literature. According to Arndt,[2] Erhlich and his pupil Pinkus were the first to show that lymphatic leukemia and pseudoleukemic processes were the same. Elsner [3] and Sternberg both stated that the transition of primary pseudoleukemia to leukemia is possible and occasionally occurs. Goeckerman and Montgomery [4] cited cases in which mycosis fungoides has changed to lymphosarcoma. They reported a case suggestive of this change. Bunting and Yates expressed the belief that lymphogranuloma can become transformed into sarcoma, and Warthin [5] maintained that it

---

Read before the North Pacific Society of Internal Medicine, Seattle, March 17, 1934.

1. Keim, H. L.: Universal Leukemia Cutis, Arch. Dermat. & Syph. **10**:579 (Nov.) 1924.

2. Arndt, G.: Diseases and New Growths of Lymphatic Origin, J. A. M. A. **63**:1268 (Oct. 10) 1914.

3. Elsner, H. L.: Prognosis of Internal Diseases, in Monographic-Medicine, New York, D. Appleton & Company, 1916, vol. 6, p. 536.

4. Goeckerman, W. H., and Montgomery, H.: Cutaneous Lymphoblastoma: Report of Two Unusual Cases, Arch. Dermat. & Syph. **24**:383 (Sept.) 1931.

5. Warthin, A. S., in Osler, W., and McCrae, T.: Modern Medicine, Its Theory and Practice, ed. 3, Philadelphia, Lea & Febiger, 1925-1927, vol. 1, pt. 2, chap. 6, p. 199.

can change into leukemia. Cases have been reported in which the condition could not be classified even after complete autopsy and on which different pathologists have expressed widely divergent opinions. Our case is interesting from the standpoint of the protean clinical manifestations and instructive from the standpoint of the pathologic changes.

REPORT OF CASE

History.—The patient was first seen in August 1928, in consultation with Dr. J. E. Ettelson, who made the diagnosis of lymphoblastoma cutis. She was a widow, 60 years of age. Her chief complaint was an itching eruption of the skin of two years' duration. It began in 1926 with two red, scaly patches on the inner side of the thighs and gradually spread to involve the entire skin. She felt well in every other way and complained of no symptoms referable to the gastro-intestinal, genito-urinary, cardiorespiratory or nervous systems. Her entire skin was peeling and gave her almost intolerable discomfort from the intense itching. Her family and her personal history were entirely negative.

Examination.—Physical examination revealed a well nourished and well preserved woman. There was a generalized, scaly, erythematous dermatitis. The color was dull red to reddish brown. The exfoliation was of a mild type with slightly adherent scales. The skin was thickened and firm to the touch. It had a pliable, leathery feel. The gluteal and other skin folds were greatly exaggerated. The results of examination of the heart and lungs and those of other physical examinations were entirely negative with the exception of the discovery of a moderate enlargement of the cervical and left axillary lymph glands, which were the size of small walnuts, firm, discrete and not tender. The liver and the spleen showed no perceptible enlargement. The roentgenogram of the chest showed no mediastinal enlargement or other pathologic changes. A complete gastro-intestinal roentgen examination, including a Cole-Graham study of the gallbladder, gave negative results. The basal metabolic rate was —3. The urine was entirely normal on several examinations. The acids of the stomach showed a free hydrochloric acid value of 39 and a total acidity of 66. The amount of bilirubin in the serum was normal. The Wassermann reaction was negative. The urea nitrogen content of the blood was 15.5 mg. per hundred cubic centimeters, and the sugar content was 100 mg. The eyegrounds showed no changes.

The chief scientific interest in the patient at that time lay in the blood counts and the adenopathy. There was a persistently high lymphocyte count, ranging up to 79 per cent, with a highest total count of 26,000. A few lymphoblasts were consistently present. Table 1 is a record of the different blood counts made during the patient's stay in the hospital as well as of subsequent counts made frequently during the course of the disease.

Pathologic Report.—Owing to the atypical blood count when the patient was first seen in 1928, it was deemed advisable to remove a gland for microscopic examination. This was done on Sept. 8, 1928. The following is the pathologic report by Dr. H. H. Foskett:

"The specimen consisted of fragments of a lymph node measuring 2 by 4 cm. with an overlying area of skin. It was of a soft, homogeneous consistency. Surfaces made by sectioning revealed a homogeneous, grayish, cellular tissue. The gland was smoothly encapsulated.

"Microscopic sections of the gland revealed hyperplasia of lymphoid cells somewhat larger than normal lymphocytes. This hyperplasia was of sufficient extent to obliterate all the normal markings of the lymph node. There was a peculiar proliferation of endothelial cells of the capillary walls. There were no mitotic figures. There was no evidence of fibrosis or hemorrhage. The skin showed an accumulation of lymphocytes in the subcutaneous tissues with a marked hyperplasia of the lymphoid tissue of the papillary layer of the skin. The hyperplasia consisted of an accumulation of lymphocytes, lymphoblasts and occasional plasma cells. There was no apparent thickening of the stratum corneum of the skin.

TABLE 1.—*Record of Blood Counts Made During a Five Year Period*

Date	Red Blood Cells, Thousands	White Blood Cells	Hemoglobin, Percentage	Polymorphonuclear Neutrophils, Percentage	Polymorphonuclear Eosinophils, Percentage	Polymorphonuclear Basophils, Percentage	Lymphocytes, Percentage	Cells Not Classified, Percentage	Lymphoblasts or Mononuclears, Percentage	Rieder Cells, Percentage
8/31/28	4,700	18,700	95	25	1	1	68	5	..	..
9/ 1/28	.....	20,600	..	14	1	..	70	18	..	..
9/ 2/28	.....	18,200	..	18	2	..	79	1	..	..
9/ 3/28	.....	12,000	..	20	..	..	70	10	..	..
9/ 4/28	.....	16,400	..	17	..	..	74	8	..	1
9/ 9/28	5,200	26,000	100	24	..	..	70	6	..	..
10/ 1/28	4,500	10,000	89	20	5	..	75	..	..	..
11/12/28	4,600	13,000	90	26	3	..	70	1	..	..
12/13/28	4,800	23,000	87	33	4	..	63	..	..	..
3/11/29	4,900	14,000	100	38	2	1	59	..	..	..
6/15/29	4,300	9,400	..	72	..	..	26	..	2	..
7/ 8/29	4,700	6,600	95	64	..	..	34	..	2	..
9/ 5/29	4,800	7,000	95	68	2	..	29	1	..	..
11/12/29	4,900	7,000	90	64	1	..	28	2	5	..
12/24/30	4,800	8,800	92	60	2	..	34	..	4	..
3/21/31	5,200	6,700	100	58	1	..	38	3	..	..
8/15/31	5,500	6,600	90	55	3	..	37	2	1	..
1/ 8/32	3,900	4,800	88	..	..	..	..	..	..	..
1/11/32	.....	5,700	..	57	1	..	42	..	..	..
9/19/32	.....	7,250	91	64	1	..	35	..	..	..
5/25/33	3,900	7,600	68	30	4	..	66	..	..	..
5/26/33	.....	8,500	..	..	..	..	..	..	..	..
9/18/33	.....	13,500	..	42	1	..	50	..	2	5

"The diagnosis is chronic lymphatic leukemia with hyperplasia of lymphoid cells involving both the lymph nodes and the cutaneous lymphoid tissue."

Course.—The patient left the hospital in 1928 and was given no treatment other than local applications for the dermatitis and intramuscular injections of sodium cacodylate. During 1929, 1930 and part of 1931 she enjoyed good health and took several long motor trips. The exfoliative dermatitis disappeared, and the swelling of the glands subsided, but there was a red, glazed appearance of the skin of the face. Erythematous rashes appeared from time to time on the neck and chest. There was also mild pruritus. The spleen was never palpable. In the winter of 1931 the exfoliative dermatitis reappeared and continued throughout 1932 and 1933. Enlargement of the glands again appeared in the neck, axillae and groins. The exfoliation was so intense that each morning a cupful of scales was taken from the bed clothing. Neither injections of sodium cacodylate nor roentgen therapy affected the cutaneous lesions. In the spring of 1933 flat purplish-red tumor-like masses began to appear in the skin, first in the groins and then

under the breasts, in the popliteal space, about the umbilicus and in the gluteal folds (figs. 1, 2 and 3). They varied from the size of a nickel up to the size of a quarter and were firm and not tender. The erythema faded on pressure. The epidermis over the growths was intact, although it was thin and glazed-looking. The nodules increased in size and number up to the time of death but did not ulcerate.

Fig. 1.—Tumor masses on posterior surface of both thighs. Note the leathery texture of the skin and the deepened gluteal folds.

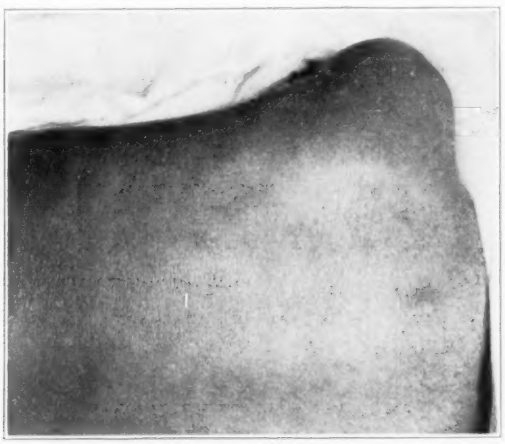


Fig. 2.—Photograph showing typical exfoliation and a cutaneous tumor in the left interscapular region.

Coincident with the appearance of the tumors in the skin, the patient had a bout of high temperature resembling the Pel-Ebstein type of fever (fig. 4). Her temperature rose as high as 106.4 F., with prostrating chills and drenching sweats, and would drop to subnormal within a few hours. The fever lasted ten days. It was accompanied by bloating and severe constipation. The white blood cell count remained low, and all laboratory findings during the bout of fever were

negative, including those from blood cultures. Three months later she again showed fever, of a milder degree, which lasted until the time of her death, but this time there was an intractable diarrhea. Three weeks before her death the white blood cell count was 13,500, with 42 per cent polymorphonuclears, 50 per cent lymphocytes, 1 per cent eosinophils and 7 per cent lymphoblastic cells. In contrast to what was observed during the remission of the disease, the lymphocytic element had again become predominant. There were many immature cells with large nuclei containing several nucleoli and a thin ring of heavily staining protoplasm. These cells gave a negative reaction to peroxidase and were considered to be lymphoblasts.

Three weeks before death the patient began to fail rapidly. She lost weight and strength and showed an icteric pallor. She became bedridden. The cutaneous tumors became especially prominent about the umbilicus. The spleen showed a tremendous enlargement. It was hard, fairly smooth and very tender. It extended almost down to the umbilicus. The liver was barely palpable. On October 4 the patient complained of pain in the left hypochondrium on deep inspiration.

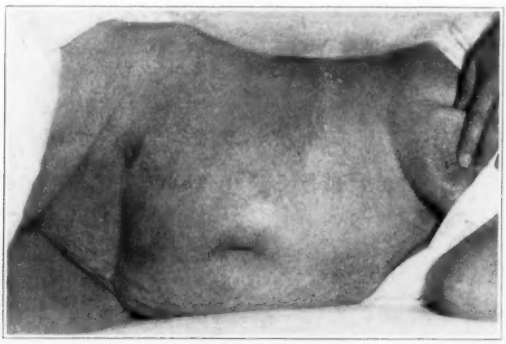


Fig. 3.—Tumors on the abdominal skin; a large tumor near the umbilicus.

There was a rise in temperature with superficial tenderness of the spleen. A friction rub was heard, and a diagnosis of perisplenitis was made. On October 8 there was extreme nausea, and purpuric spots appeared on the face and neck. On October 10 the patient became comatose. The respiratory rate dropped to 6 per minute, and the pulse was weak and thready. Death occurred on this date.

Autopsy.—The skin presented the appearance described earlier in the clinical record. The axillary, inguinal and cervical lymph glands were considerably enlarged. Many cutaneous and subcutaneous nodules could be felt; one, for example, measuring 2 cm. in diameter, in the right breast, was elevated to about 5 mm. above the level of the surrounding skin. Another nodule could be felt to the right of and above the umbilicus. This nodule measured 7 cm. in diameter, and when it was sectioned it was found to be about 2 cm. in thickness and presented a whitish, translucent surface. The skin had an icteric hue. The abdomen contained an excess of peritoneal fluid, greenish with flecks of fibrin. The liver weighed 1,675 Gm., and had a mottled yellowish color, with greenish, irregular, anastomosing striations separating the yellow areas. It was firm. The spleen

weighed 1,175 Gm. The diaphragmatic surface was adherent to the diaphragm by fresh fibrinous adhesions. Three large anemic infarcts were present. The spleen was firm. On section it presented a brownish-red surface with irregular pale areas about 2 to 3 mm. in diameter. The kidneys were normal in size and macroscopic appearance. The iliac, aortic and hepatic lymph nodes were enlarged and discrete. No areas of necrosis or hemorrhage were seen. The cut surface presented a whitish, opaque appearance. The mesenteric and mediastinal nodes were not enlarged. The marrow of the sternum, ribs and vertebrae was reddish and soft.

Histologically, the nodules in the skin (figs. 5 and 6) were composed of rather closely packed cells. The predominating cell resembled a large lymphocyte with a large nucleus rich in chromatin and with prominent nucleoli but with scanty cytoplasm. There was, however, great variation in the size of the nucleus and

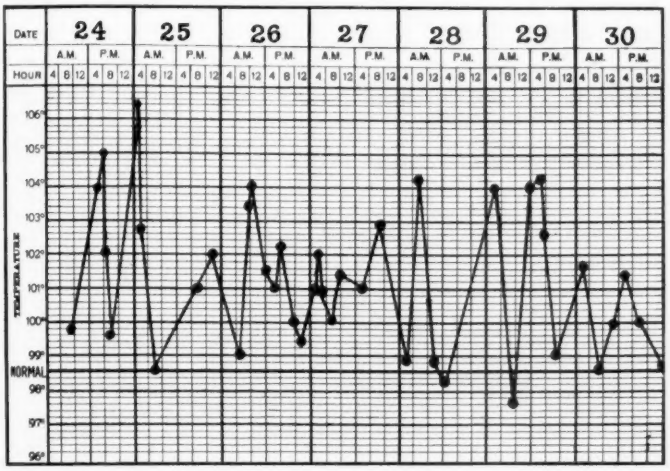


Fig. 4.—Chart of temperature during an attack of fever in May 1933 coincident with the appearance of cutaneous tumors.

the relative amount of cytoplasm. Cells as large as 20 microns in diameter were frequently seen. These had large nuclei and a small amount of cytoplasm. The chromatin was arranged in a dense peripheral ring, and large nucleoli were present. Small cells resembling lymphocytes were also numerous. Eosinophils and plasma cells were present. Large spindle-shaped cells with vesicular nuclei, forming irregular nests, were also a prominent feature. The stroma was scanty. There was no detectable *Grenz* zone or free zone, such as is described for leukemia, but the infiltration involved all the layers of the corium and affected the papillae. The epidermis was greatly thinned over the papillae, while the interpapillary pegs were lengthened. The normal structure of the lymph nodes was extensively altered (figs. 7 and 8). Only occasionally could the peripheral sinus be recognized. No lymph follicles or secondary nodules were seen. The sections had a homogeneous appearance, the normal structure of the gland being replaced by a dense accumu-

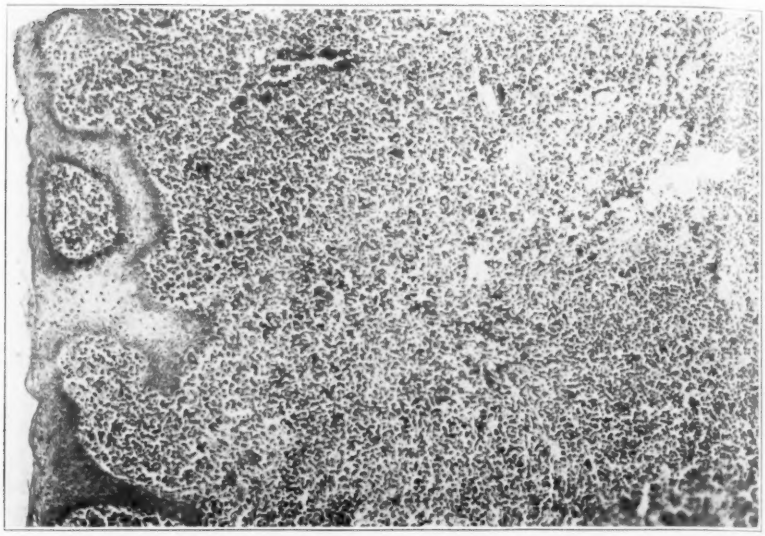


Fig. 5.—Photomicrograph of skin over a nodule. The entire corium is involved in desquamation and acanthosis. There is hyperplasia of the lymphoid tissue of the papillary layer consisting of lymphocytes, lymphoblasts and occasional plasma cells. In some areas these cells have infiltrated into the more superficial portion of the skin. The "free zone" of the cutis is absent.

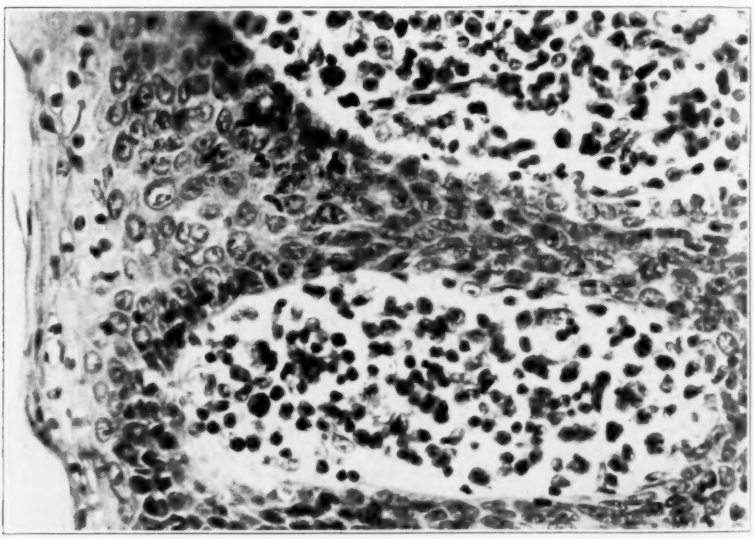


Fig. 6.—A section of the skin over the edge of a nodule under high power magnification.

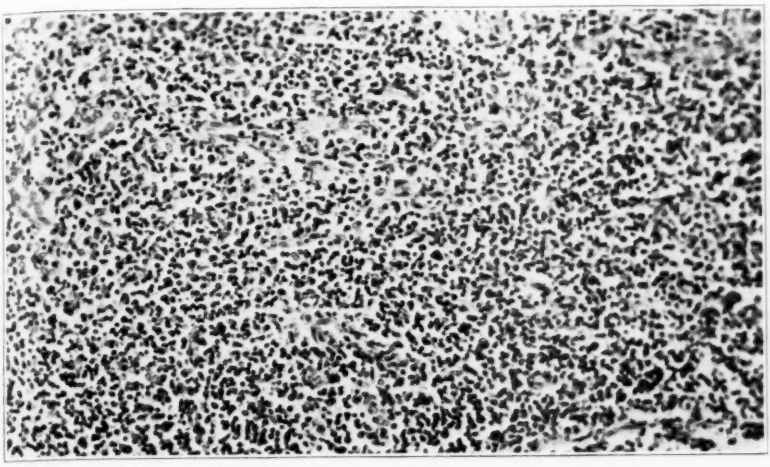


Fig. 7.—Photomicrograph of a section of a lymph node showing a dense accumulation of lymphocytes in the medullary cords and also large endothelial cells.

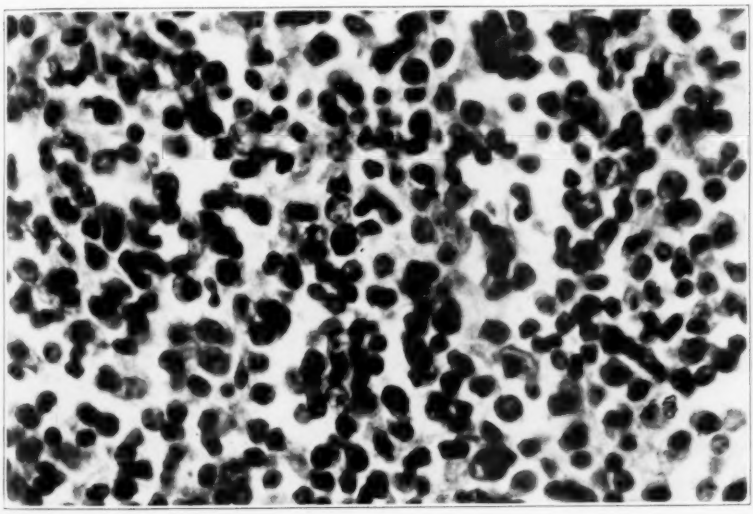


Fig. 8.—Section of a lymph node under high magnification.

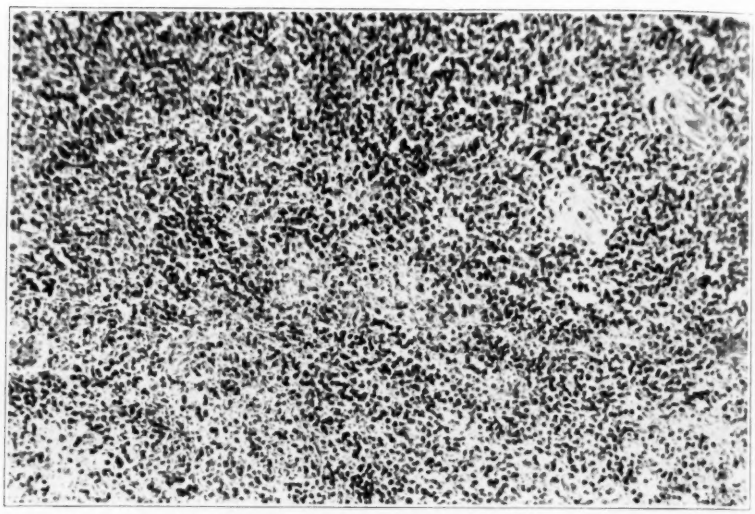


Fig. 9.—Section of the spleen under low magnification. The section shows considerable fibrosis of the pulp. A malpighian corpuscle is shown at the right.

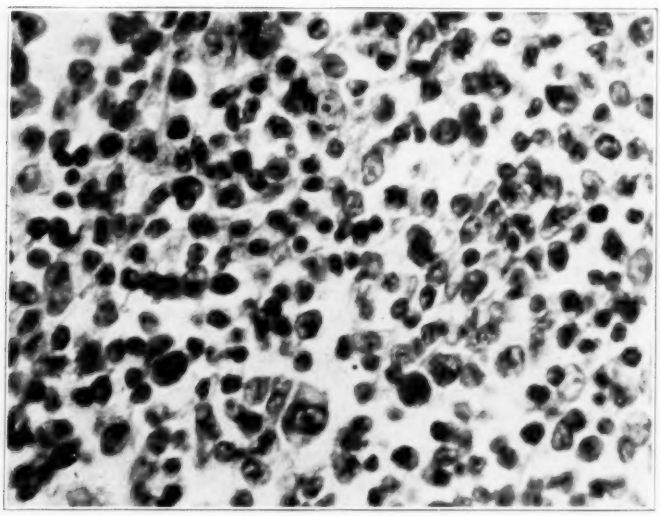


Fig. 10.—Photomicrograph of tissue from spleen under high magnification. This section shows the dense accumulation of lymphocytes of various sizes in the sinuses of the spleen.

lation of cells having the same appearance as those described in the nodules in the skin. There was marked endothelial hyperplasia and an occasional large phagocytic cell containing red cells. Fragments of nuclei were seen. Scattered eosinophils were present. The malpighian corpuscles of the spleen were reduced to a small rim around the central artery (figs. 9 and 10). The sinuses of the pulp were filled with the cellular infiltrate already described for the other organs. Many areas of fibrosis were present. The amount of blood in the pulp varied considerably in different areas. Eosinophils and plasma cells were numerous. The liver (fig. 11) showed marked periportal fatty degeneration and infiltration by round cells. The smears of marrow from the sternum and ribs showed active formation of red and granulocytic cells. The other organs were essentially normal.

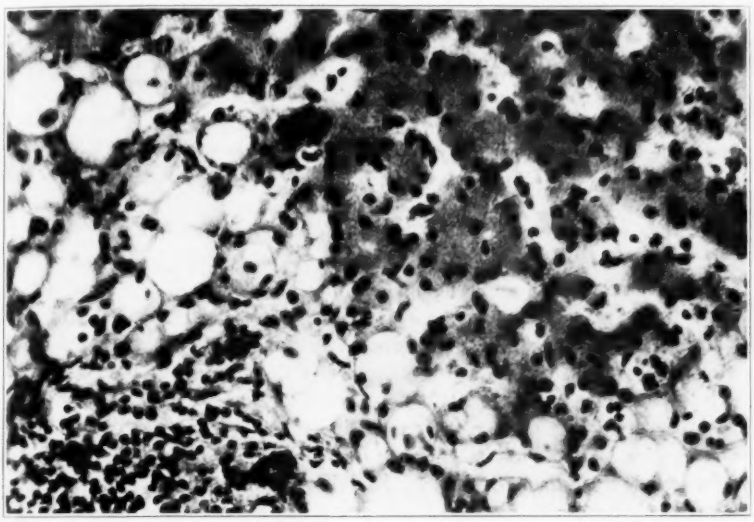


Fig. 11.—Section from liver showing periportal fatty degeneration and the accumulation of round cells.

COMMENT

In the lymphoblastomatous group of diseases two types of cutaneous disease are recognized: first, a nonspecific type including exfoliative erythroderma, generalized pruritus, lichenification, urticaria, bullous eruption and prurigo-like nodules, and second, the specific type of true nodular infiltration, which may be well localized or disseminated. It is of particular interest to recognize that these so-called nonspecific lesions do exist. They are of toxic origin and occur in from 15 to 40 per cent of cases, according to Cole. They may, as in the case reported in this paper, precede the formation of cutaneous nodules by months or even years. Chronic exfoliative dermatitis may be only a symptom of some

fatal underlying systemic disease, even in the absence of changes in the glands or blood. Cases exemplifying this fact have been reported by Miller,[6] and Arndt,[7] Doesseker, Breitkopff, Hoffman, Bacher, Sarfeld, and others. Nekam in 1899 reported four cases of what he considered to be undoubted leukemic infiltration of the skin, but Whitfield [8] cast some doubt on this diagnosis and stated that the condition is extremely rare. Miller [6] stated that Grosz in 1906 undoubtedly described the first example of a true lymphogranulomatous infiltration of the skin. Since then cases have been reported by Brunsgaard, Sibley, Hirshfeld, Alderson, Fox and others. Miller [6] stated, in a review of the literature, that only a few of these cases are instances of true lymphogranuloma. The others are simply extensions from neighboring glands or deep subcutaneous lesions. In his series of fifty-five cases, collected at the University of California Hospital, only one showed true specific infiltration of the skin. In this case at least one third of the surface of the body was covered with raised, infiltrated plaques at the time of death. The patient was a man, aged 34, with enlarged axillary and inguinal lymph glands and a large spleen. His blood count was 18,000, with 65 per cent polymorphonuclears, 5 per cent eosinophils, 7 per cent lymphocytes and 23 per cent large mononuclear lymphocytes.

Rulison [9] reported a case of Hodgkin's disease of the skin and reviewed the literature, stating that up to 1930 there had been reported only thirty-one accepted cases and that most of these were characterized by the formation of tumors in the skin. He stated that in 10 per cent of all cases of Hodgkin's disease cutaneous manifestations are the first symptoms and are of toxic origin. His patient was a woman aged 38. An erythematomacular eruption without exfoliation preceded the adenopathy by two months. Biopsy of the skin and glands showed the microscopic appearance typical of Hodgkin's disease in both specimens. The blood count was 11,900, with 62 per cent polymorphonuclears, 1 per cent eosinophils, 6 per cent large lymphocytes and 31 per cent small lymphocytes.

Elsner [3] and Whitfield [8] expressed the belief that multiple cutaneous nodules are not uncommon in this disease. Whitfield examined material taken in two such cases in which late in the disease there was a slow formation of nodules in the skin. They flattened out the epidermis, producing a tense, purplish-red, discolored infiltration. They were firm,

6. Miller, H. E.: Lymphogranulomatosis Cutis: Hodgkin's Disease, Arch. Dermat. & Syph. **17**:156 (Feb.) 1928.

7. Arndt, G.: Dermat. Ztschr. **18**:1139, 1911.

8. Whitfield, A., quoted in Allbutt, T. C., and Rolleston, H. D.: A System of Medicine by Many Writers, New York, The Macmillan Company, 1911, vol. 9, p. 328.

9. Rulison, R. H.: Hodgkin's Disease of Skin: Report of Case, Arch. Dermat. & Syph. **22**:389 (Sept.) 1930.

and no yellow transparency could be observed on pressing out the blood. Whitfield [8] stated that his description tallies closely with the cutaneous symptoms described in true leukemia.

Ketron and Gay [10] reported a case of universal lymphatic leukemia of the skin in a man aged 63. Their patient showed the nonspecific type of lesion, with a typical blood count and typical lymphocytic infiltration of the epidermis. This was the sixth case reported up to 1923, the others having been reported by Riehl,[11] Linser,[12] Rodler-Zipkin,[13] Arndt [7] and Bernhardt.[14] Bernhardt's case was the only one in which there were nodules or tumors in the skin. A summary of all the cases reported up to 1923 is given from Ketron and Gay's [10] article (table 2). To these must now be added Keim's [1] case reported in 1924 and Schmidt's [15] case reported in 1931. Ketron and Gay [10] expressed the belief that the apparent rarity of cases reported is due in part to insufficient studies of the blood in cases of universal dermatitis and perhaps also to the fact that many of the cases reported as instances of pseudoleukemia were really cases of leukemia in a stage of remission.

According to Arndt [2] the typical picture in leukemia cutis is a lymphocytic infiltration with the large lymphocytes and lymphoblasts predominating over the small lymphocytes. The circumscribed lymphadenoses are almost entirely composed of small lymphocytes. When the rash is universal, numerous mitoses are found. Arndt [2] further described a characteristic zone in the papillary layer which is free from infiltration. He stated that in large tumors there may be an absence of hair follicles and sebaceous and sweat glands. Ketron and Gay [10] expressed the belief that the cellular exudate is not confined to any one type of lymphocytic cell but may vary according to the age of the cell and perhaps according to further development in the tissues. Furthermore, it is extremely difficult to differentiate the cells when they are so closely packed together.

In 1931 Schmidt [15] reported a case of leukemia cutis in a child, aged 2 years, who showed numerous flat, button-like lesions in the skin, which were freely movable, painless and the color of a bruise. She died

10. Ketron, L. W., and Gay, L. N.: Universal Lymphatic Leukemia of Skin, Bull. Johns Hopkins Hosp. **34**:404 (Dec.) 1923.

11. Riehl, G.: Leukemia Cutis, Wien. klin. Wchnschr. **6**:6, 1893.

12. Linser, P.: Beiträge zur Frage der Hautveränderungen bei Pseudoleukämie, Arch. f. Dermat. u. Syph. **80**:3, 1906.

13. Rodler-Zipkin, R.: Ueber einem Fall von akuter grosszelliger lymphatischer Leukämie mit generalisierter Hauterkrankung, Virchows Arch. f. path. Anat. **197**:135, 1909.

14. Bernhardt, R.: Ueber die Leukämie der Haut, Arch. f. Dermat. u. Syph. **120**:17, 1914.

15. Schmidt, F. R.: Leukemia Cutis: Report of a Case, Arch. Dermat. & Syph. **24**:587 (Oct.) 1931.

TABLE 2.—*Summary of Data on Reported Cases of Universal Lymphadenosis of the Skin* *

Author	Sex	Age	Duration	Beginning	Character of Eruption	Glands	Liver and Spleen	Greatest White Cell Count	Percentage of Lymphocytes in Blood	Autopsy Findings	Histologic Appearance of Skin
Riehl [11]	F	57	4 yrs.	Eczematous itching patches on back	Generalized reddening and swelling with thickening of skin of face, neck and inguinal regions; surface generally dry with moderate scaling; here and there moist areas	Size of pea to that of apple	Distinctly enlarged	Proportion of white cells to red cells, 1:24	.....	Characteristic changes of lymphatic leukemia	Infiltration of various-sized round cells with large nuclei and scant protoplasm; numerous eosinophils
Lisner [12]	M	58	1½ yrs.	Vesicular, reddish, itching eruption in bend of joints	Generalized thickening and reddening of skin which was covered with scales; excoriations over buttocks; skin bled easily	Enlarged to size of apple	Enlarged	47,000	94%	.....	Dense infiltration in the cutis composed for the most part of small lymphocytes; a few mast cells; no eosinophils or plasma cells
Rodler-Zipkin [12]	F	41	3 yrs. or more	Itching reddish patches	Generalized diffuse reddening, scaling and thickening of skin; dry and like parchment	Markedly enlarged	Enlarged	44,000	Large 28% Small 15%	Infiltration of liver and spleen with large lymphocytes	Cutis densely infiltrated with large lymphocytes; giant cells numerous; a few mast and plasma cells; no eosinophils
Arndt [7]	M	55	8 mos.	Severe itching with generalized reddening and swelling of skin	Generalized diffuse reddening and thickening of skin; moderate scaling, moist areas here and there	Enlarged to size of child's fist	Not palpable	800,000	78%	Leukemic changes in internal organs	Dense lymphatic infiltration in cutis with large lymphoblasts and lymphocytes predominating; giant cells present; also a few mast cells and eosinophils
Bernhardt [14]	F	57	2½ yrs.	Reddish, scaly itching eruption on scalp	Generalized thickening and reddening of the skin with abundant scale formation, areas of atrophy, nodules and warty formation	Enlarged	Spleen enlarged	54,000	Large 12% Small 72%	.....	Dense infiltration of small lymphocytes in cutis; a few mast and eosinophil cells
Ketron and Gay [10]	M	63	10 mos.	Intense itching and reddening of legs	Generalized thickening and reddening of skin; profuse scaling; skin bled easily; warty formation on ankles	Size of English walnut	Spleen enlarged but not palpable	184,000	Large 2% Small 90%	.....	Dense infiltration of cutis by small lymphocytes with moderate number of fixed tissue cells; no eosinophils; numerous groups of plasma cells

* Taken from Ketron and Gay.[10]

within one year from the onset of symptoms. The glands, spleen and liver were not palpable. Nine white blood cell counts were between 3,800 and 20,000, with an average of 9,000, and showed lymphocytosis, with an average of 80 per cent. Many of the lymphoid cells in the smears resembled lymphoblasts. About one third of the lymphoid cells were blastomatous in type.

Sequeira [16] in 1921 reported three cases under the name lymphoblastic erythroderma, which he described as a disease entity apart from mycosis fungoides and leukemia. The condition in his cases was characterized by a specific change in the blood, a leathery, red, exfoliative skin and, in one case, a general adenopathy. The white blood cell counts averaged 9,500, and the differential count showed a reversal of the normal lymphocyte-neutrophil ratio. He did not believe the cases to be instances of true leukemia, because, as he stated, in true leukemia the count is higher and the relative percentage of lymphocytes is greater. In the light of knowledge from more recent articles, it is quite likely that Sequeira's cases might well have been classified as leukemia even in the absence of high white blood cell counts. Furthermore, in Sequeira's [16] opinion most cutaneous infiltrations occur in the myeloid type of leukemia. Elsner,[3] Warthin [5] and Longcope, on the other hand, stated that cutaneous nodules are relatively frequent in both acute and chronic lymphatic leukemia. Montgomery [17] also recognized dense infiltration of the skin both in lymphatic and in myelogenous leukemia. Arndt [2] contended that up to 1914 myeloid leukemia with a diffuse universal participation of the skin with typical myeloid tissue had not been observed, and certainly circumscribed involvement of the skin is extremely rare. Arzt [18] recognized a predilection of the lymphocytic tumors for the nose, cheeks, eyelids, lips, chin, ears, ear lobes and glabella, producing a facies leontina such as lepers show, although the tumors do occur also on the breasts, abdomen, scrotum and other parts of the body. Schmidt [15] stated that there have been only a few reports in the literature of lymphatic leukemia in which the diagnosis of true leukemia cutis has been supported by histologic evidence. Keim [1] said that universal leukemia cutis with general hyperplastic proliferation does not occur in myeloid leukemia, and so the term refers to a universal lymphadenosis of the skin occurring in the course of lymphatic leukemia. His patient showed an exfoliative dermatitis, papillomatous

16. Sequeira, J. H., and Panton, P. N.: Lymphoblastic Erythrodermia, Brit. J. Dermat. **33**:391 (Dec.) 1921.

17. Montgomery, H.: Exfoliative Dermatosis and Malignant Erythroderma: Value and Limitations of Histopathologic Studies, Arch. Dermat. & Syph. **27**:253 (Feb.) 1933.

18. Arzt, L.: Leukämische Erkrankungen der Haut, Wien. klin. Wchnschr. **46**:1125 (Sept. 15) 1933.

growths on the extremities, general adenopathy, a palpable liver and spleen and a blood count of 30,000, with a differential count of 28.5 per cent polymorphonuclears, 0.5 per cent eosinophils, 56.5 per cent small lymphocytes, 10 per cent large lymphocytes, and 0.5 per cent transitionals. The count later rose to 85,000, with predominance of a white cell which was a medium-sized lymphocyte with a small amount of fragile cytoplasm. In type it was about midway between the ordinary large and small lymphocytes of normal blood. The diagnosis was supported by complete autopsy.

CONCLUSION

Under the grouping of lymphoblastoma cutis are included four diseases—leukemia, Hodgkin's disease, lymphosarcoma and mycosis fungoides. They may or may not be accompanied by changes in the blood and internal organs, but all may affect the skin by actual invasion of the corium. They resemble each other so closely that differentiation is often impossible. Generalized exfoliative dermatitis is a common precursor, often preceding the formation of specific cutaneous tumors by several years. Complete remission may occur, but in all cases the disease is eventually fatal.

A case of seven years' duration has been described. There were early exfoliative dermatitis and enlargement of the lymph glands and the changes of the blood typical of lymphatic leukemia. Early biopsy confirmed this diagnosis. The patient had a remission and later presented tumors of the skin and enlargement of the spleen. The total white blood cell count remained relatively low and showed the same types of cells originally observed. There was a widespread exfoliative dermatitis, the etiology of which is always obscure and which shows the necessity of careful hematologic and histopathologic study. A survey of the literature reveals a necessarily widespread divergence of opinion as to the typical pictures of the various entities of this group.

ARRHENOBLASTOMA: A SPECIAL TYPE OF TERATOMA

REPORT OF A CASE

JAMES B. McLESTER, M.D.
BIRMINGHAM, ALA.

Since Pick,[1] in 1905, first described a tumor of the ovary closely resembling the seminiferous tubules of the testis, others, usually of more atypical structure, have been described. These growths are made up of apparently masculine tissue and influence the secondary sex characteristics in a masculine direction; but, strangely, those with the least microscopic resemblance to testis show the greatest masculinizing effect. The tumor is mildly malignant, and direct extension occurs, although true metastasis has not been reported. Originally called adenoma testiculare ovarii, it has more recently been designated arrhenoblastoma, from the Greek *arrhen*, meaning male.

The arrhenoblastoma was thought by Meyer[2] to arise from certain embryonic remains incorporated in the ovarian medulla, and he considered the microscopic appearance of the tissue to be characteristic. Novak and Long[3] recently discussed this type of tumor together with the more frequent feminizing granulosa cell tumor; they found twenty-eight cases of arrhenoblastoma of all grades of embryonic differentiation reported in the literature. Only three were reported in the American literature, and Novak and Long reported another after examination of their old pathologic material. Krock, in his discussion of the paper by Novak and Long, suggested that the tumor might be a teratoma, consisting chiefly or entirely of testicular tissue rather than the more usual elements.

I am reporting a case in this group, with evidence that the tumor was a teratoma.

---

1. Pick, L.: Ueber Adenome der männlichen und weiblichen Keimdrüse bei Hermaphroditismus verus und spurius: Nebst Bemerkungen über das endometrium-ähnliche Adenom am inneren weiblichen Genitale, Berl. klin. Wchnschr. **17**:502, 1905; quoted by Novak and Long.[3]

2. Meyer, Robert: Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characteristics, Am. J. Obst. & Gynec. **22**:697, 1931.

3. Novak, E., and Long, J. H.: Ovarian Tumors Associated with Secondary Sex Changes: Granulosa Cell Carcinoma and Arrhenoblastoma, J. A. M. A. **101**:1057 (Sept. 30) 1933.

REPORT OF CASE

History and Course.—Mrs. T. W. S., a 32 year old housewife, was first seen on Oct. 3, 1933, complaining of hoarseness, an abdominal tumor and an unusual growth of body and facial hair. Her father had died of carcinoma of the stomach. There had been no endocrine disorder and no known developmental anomaly in her family.

In the past, the patient had had no significant illness. She was a rather feminine type of woman, with a rounded body and a good complexion; her voice

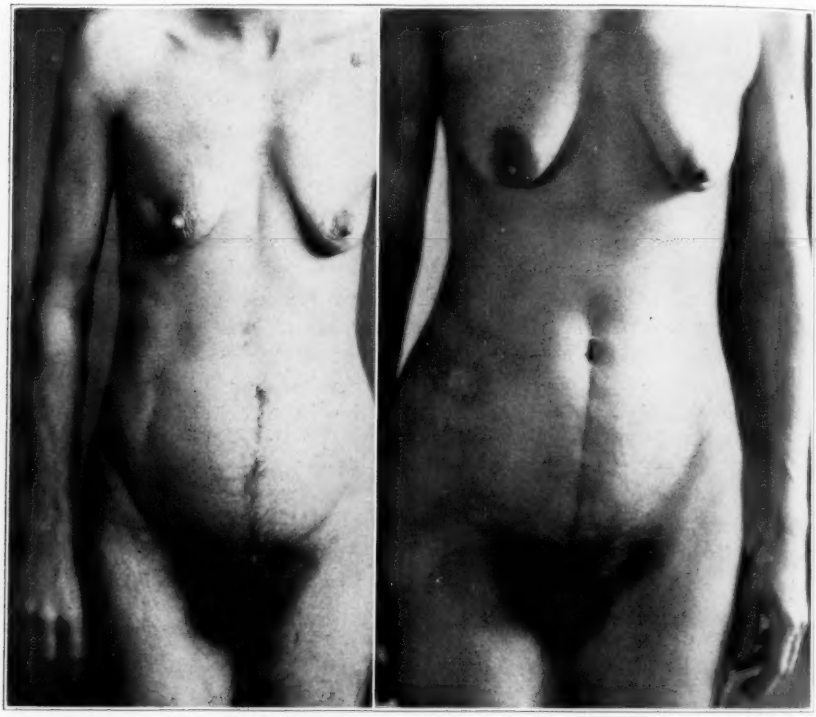


Fig. 1.—The figure on the left shows the patient on Oct. 18, 1933, before operation, with profuse masculine pubic hair and flat breasts, and that on the right, made on May 9, 1934, six months after operation, shows the pubic hair to be of feminine type and the breasts fuller. The operative scar can be seen.

was high-pitched, and the distribution of body hair was of feminine type. The menses began at 13 years, were rather profuse, lasted five days and recurred regularly every twenty-eight days. There had been seven pregnancies, the fourth and the sixth ending in miscarriage. After the birth of the first three children and after both miscarriages, the menses returned in the first month post partum. After the birth of the fourth child, the patient did not menstruate until the fifth month.

After the birth of her last child, in March 1930, the patient menstruated but twice, in the fourth and sixth months post partum. She felt tired and weak, and she could feel a mass the size of an egg in the abdomen. There was no other specific complaint. In January 1932 she began to be hoarse, particularly after talking for a long time. The body hair gradually became heavier and darker, and she began to shave, occasionally at first but finally every day. The mass slowly increased to the size of a large grapefruit, but at no time was there abdominal discomfort. In the three years the patient had lost about 15 pounds (6.8 Kg.). There was no definite change in her libido. The amenorrhea continued.

Fig. 2.—The figure on the left shows the patient on Oct. 18, 1933, before operation, four days after shaving. The beard and prominent thyroid cartilage can be seen. The figure on the right shows the patient on May 9, 1934, six months after operation, ten days after shaving. The beard cannot be seen and the face is fuller. The thyroid cartilage is still prominent.

Physical examination in October 1933 revealed the patient to be slight, with little body fat and a somewhat boyish figure. The voice was husky and changeable, like that of a boy at the age of puberty. The body hair was of masculine type, with a fairly heavy beard and coarse black hair on the arms and legs, in the axillae, around the nipples and on the abdomen. The area of pubic hair had a convex upper border and extended up to the umbilicus. The thyroid cartilage was unusually prominent. The breasts were flaccid and contained little fat. In the midline of the lower portion of the abdomen there was an irregularly spherical, firm, nontender mass about 15 cm. in diameter. It could be moved freely into

either flank without causing discomfort; when pulled into the upper portion of the abdomen it caused a "drawing" sensation in the suprapubic region. It could not be felt on pelvic examination. The uterus was in first degree retroversion, and there seemed to be no connection between it and the abdominal mass. The clitoris, measuring 3 cm. long and 1 cm. in diameter, was enlarged and erectile. Physical examination revealed no other abnormality.

Fig. 3.—The figure on the left shows the patient on Oct. 18, 1933, before operation, with profuse hair on the legs, and that on the left, made on May 9, 1934, six months after operation, shows no hair.

There was moderate secondary anemia. The basal metabolism was 36 and 41 per cent above the average on two occasions. Roentgenograms of the skull and chest showed no evidence of disease.

At operation (by Dr. S. L. Ledbetter Jr.) on Oct. 19, 1933, a tumor the size of a large grapefruit, apparently of the right ovary, was found. Adherent to its

surface was a tab of omentum. The tumor was attached to the right fallopian tube by a small ovarian pedicle; elsewhere it was unattached. There was no evidence of extension other than that in the adherent omentum. On the left side were a nodule 8 mm. in diameter in the tube and two small masses, the larger, 4 cm. in diameter, connected with the ovary by a cordlike band 2 cm. long. The other was connected to this one by a cord and also to the tube by a small cordlike band. The left ovary was of normal size, hard, pale and sclerotic and contained no visible follicles. The uterus was of normal size. The large tumor of the right ovary was removed with the tube and the omental attachment, and the left tube with the small nodule, and the two small masses were removed. The left ovary and the uterus were left in place.

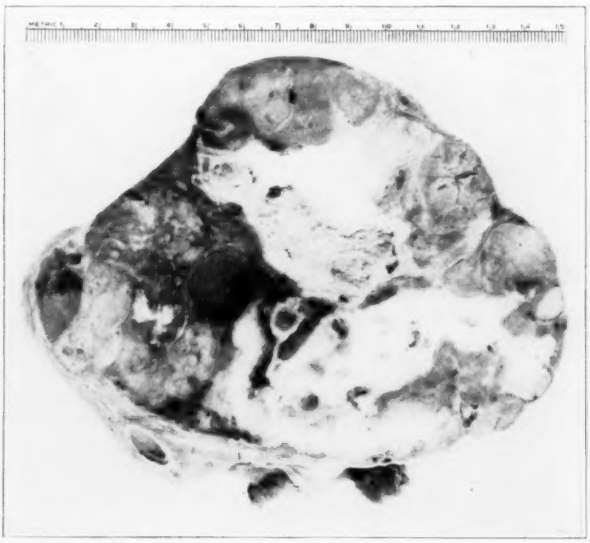


Fig. 4.—The bisected tumor. The oviduct is suspended below. Surviving ovarian tissue can be seen along the lower left-hand margin of the mass.

The postoperative course was marked by a gradual return of feminine characteristics. On about the tenth day the patient's voice was higher-pitched, and talking was easier. Though it becomes husky on occasions, her voice has continued to be better. On the twenty-ninth postoperative day a normal menstrual period began. Since then the menses have been on rare occasions slightly irregular and somewhat less profuse than formerly but otherwise normal. There was little change in the body hair until late in February 1934, four months after, when it was noticeably less heavy and was falling out in large quantities. In April, the sixth postoperative month, the pubic hair was of feminine distribution; hair on the abdomen and chest had disappeared; the amount of hair on the arms and legs was less, and a week after shaving the beard was scarcely noticeable. At this time the skin was more delicate, the face and figure were somewhat rounder and the breasts were fuller. The thyroid cartilage was still prominent. The clitoris had

become about one third its preoperative size, and the uterus was in a normal anterior position. The basal metabolism had fallen to normal after remaining persistently in the neighborhood of 20 per cent above that figure for five months. The right kidney was palpable for the first time. There were no symptoms referable to it. At no time has there been elevation of the pulse rate, sweating or other evidence of thyroid disease. A year after operation the patient continued to improve, and there was no evidence of recurrence of the tumor.

Pathologic Examination (From the Report of Dr. George S. Graham).—The tissue was fixed in Zenker's fluid, Orth's fluid and solution of formaldehyde. Paraffin sections were stained with hematoxylin and eosin and iron and hematoxylin and according to Mallory's eosin and methylene blue, phosphotungstic acid and hematoxylin and aniline blue methods for staining connective tissue.

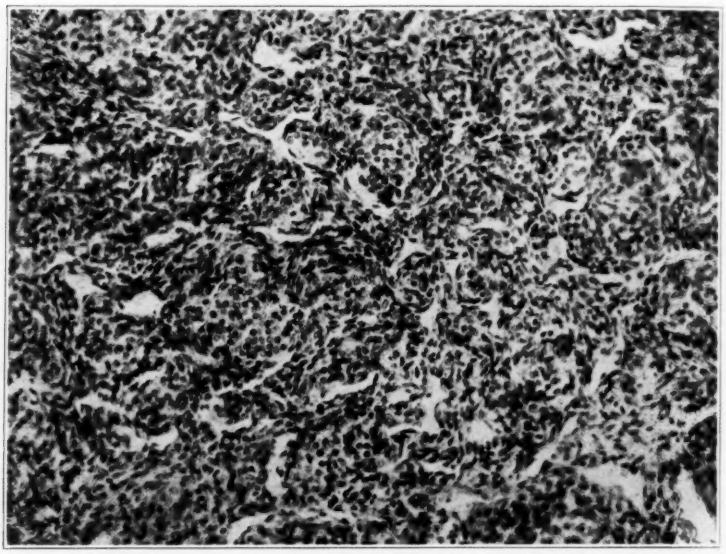


Fig. 5.—A typical low power magnification of a denser portion of the ovarian tumor; × 150.

Scarlet red was applied to frozen sections and to heavily chromated material fixed in solution of formaldehyde (method of Ciaccio).

The main specimen (fig. 4) was an irregularly ovoid mass, with a smooth opaque capsule of ovarian type. It measured 17 cm. in greatest diameter and weighed 930 Gm. At the broader end was an adherent fragment of omentum. Suspended along one side was an oviduct, free from gross lesions. A small nodulation with a furrowed surface, which on section presented the characteristics of ovarian tissue, projected from the mass alongside the ligament to the tube. An opaque white membrane outlined a cyst about 1 cm. in diameter. The remainder of the mass consisted of soft opaque yellow tissue with an occasional admixture of grayish-white tissue, occasionally translucent and moist. There were scattered hemorrhagic foci. Thin septums sometimes divided the mass into lobular fields.

Beneath the omental adhesion a wide area of firm yellow necrotic tissue extended deeply into the mass, and there were frequent smaller areas of necrosis. At one place there was a cyst 6 cm. in diameter. Its lining wall was in part smooth and in part covered by closely placed translucent secondary cysts.

The tumor tissue was made up chiefly of cells of two morphologic types, one rounded or polygonal and the other fusiform (figs. 5, 6 and 7). Transitional examples suggested, however, that these were phases of a single basic cell. In the fusiform type the nucleus was elongated and the cytoplasm scanty. It often resembled a fibroblast. The polygonal cell was larger, with a sharply outlined cell body. The rounded nucleus contained coarse chromatin particles and a prominent nucleolus. Characteristically, the delicately reticulated cytoplasm was abundant, with a central, more compact, finely granular portion and a peripheral paler

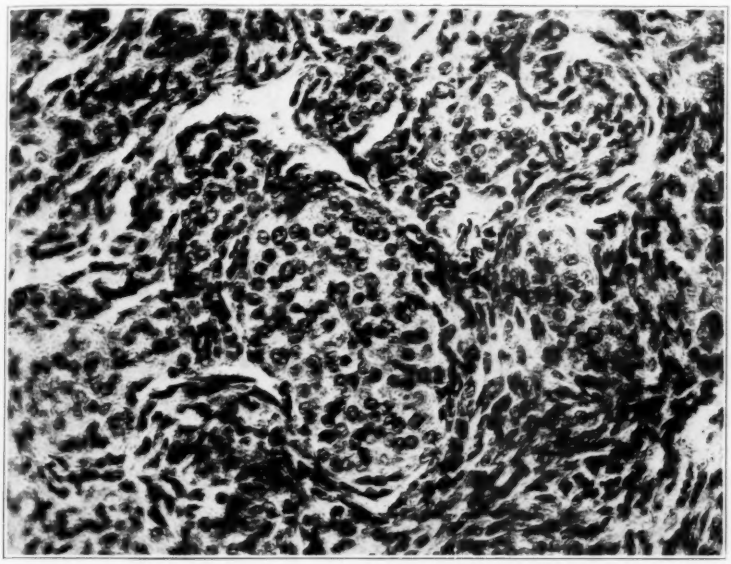


Fig. 6.—A high power magnification, showing the arrangement of the two cell types observed in the tumor and the intimate relationship of the large cell clumps to the plexiform sinusoidal blood vessels; × 300.

zone of attenuated or vacuolated structure. In some cells there were coarse granulations and irregular or elongated particles of small size, the exact nature of which could not be made out. Frequent inclusion bodies appeared as small eosin-stained, occasionally rather refractile, globules. Furthering the suggestion of the glandular nature of the cell was its arrangement in clumps or columns, outlined by a plexiform arrangement of thin-walled blood vessels. In areas of looser structure the polygonal cells were occasionally present alone. In more compact fields the peripheral cells of the columns often flattened out into a capsular layer of fusiform elements. Again, the fusiform cells predominated, and rarely they completely replaced the other type over a limited area. Sharpest contrast was afforded when islands of large, coarsely granular cells were isolated

in the more compact areas (fig. 7). Mitotic figures were numerous but most common in the fusiform cells. There were frequent necrotic areas, some of them hemorrhagic. In many fields, especially at the margins of necrotic foci, the tumor cells were fewer and appeared as sharply outlined anastomosing columns, from one to several units wide, embedded in a highly vascular collagenous stroma of varying density. The columns were widely separated in some places, and the fibrillar stroma was often infiltrated by a fluid material containing many fine hyaline eosin-staining droplets. The tumor cells of the columns were of the rounded type and varied considerably in size and cytoplasmic contents.

There was a patchy distribution of fat throughout the tumor. It occurred within the cytoplasm of the tumor cells, almost always in the rounded or polygonal type (fig. 8). In the more compact fields there was little fat, but it became

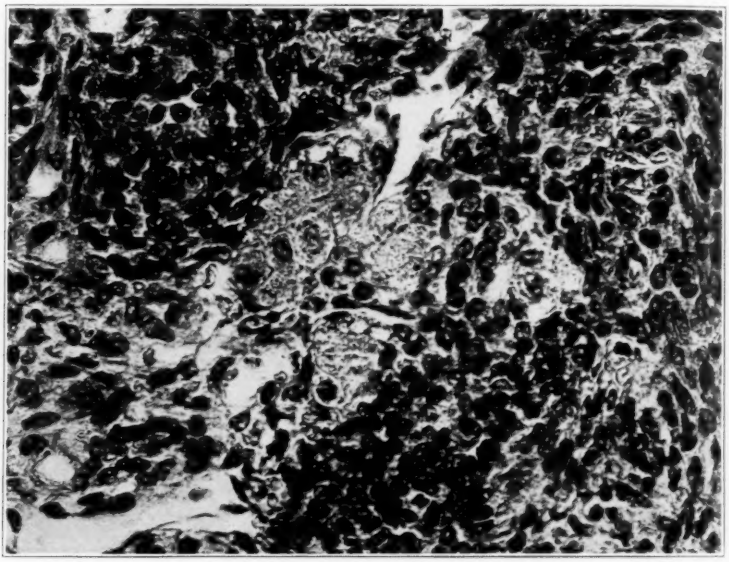


Fig. 7.—A clump of large cells of the tumor, showing more clearly their gland-like structure and arrangement; × 300.

more common in the looser areas, where in some places most of the cells were thickly dotted with it. The fat particles exhibited a peculiar morphologic picture. For the most part they appeared as a thin crescent partially outlining a vacuole or globule of unstained material or formed a delicate circlet, crescentically thickened in from a third to a half of its circumference, completely enclosing such a body. Some appeared as the usual solid globules, but this may have been due to the angle from which they were observed. Most of the bodies were small, and many of them were crowded into the cytoplasmic substance of single tumor cells, but occasional bodies were double or triple the average size. The larger bodies, like the smaller circular ones, appeared as signet-rings or hollow spheres. They were sometimes present within cells undergoing mitotic division. The appearance

was the same in a material fixed in a solution of formaldehyde, whether in frozen sections or in paraffin sections of chromated blocks.

The large cyst lying within the tumor was lined by a single layer of columnar epithelium with mucus-producing cells (fig. 9). Typical goblet cells were present. The epithelium was supported on a shallow zone of loose stroma containing many small cysts. Their lining epithelium was sometimes mucus-producing, in some instances free from mucus and in occasional cases flattened. The tumor cells at times infiltrated the stroma between the cysts.

The left oviduct was 7.5 cm. long and 0.8 cm. in maximum diameter. At the ampulla there was a serous cyst 0.2 cm. in diameter lined with ciliated columnar epithelium. Within the wall of the tube was a firm, yellowish-white nodule,

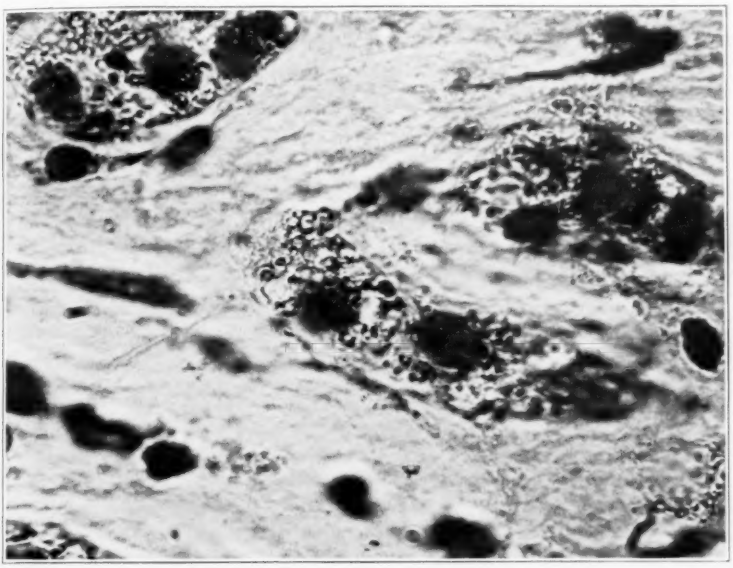


Fig. 8.—Tumor cells from a looser area cut by frozen section and stained with scarlet red and hematoxylin. The cytoplasm is crowded with refractile globular bodies outlined by crescentic or signet-ring fat particles that appear black in the photograph; × 700.

0.6 cm. in diameter (fig. 10). It consisted in a rich plexus of narrow channels supported in a mesh of fibrous tissue and lined usually by a single layer of flattened cells. Rarely these cells became higher or even columnar and definitely epithelial. The nodule filled the whole thickness of the wall of the tube on one side. It bulged into the tubal lumen, where at its summit the epithelium lining the tube appeared to be in direct continuity with that lining the channels of the tumor. There was an occasional suggestion of a similar continuity with the serosal cells covering the tube. The sections of the mass presented a picture typical of the rete testis (fig. 11).

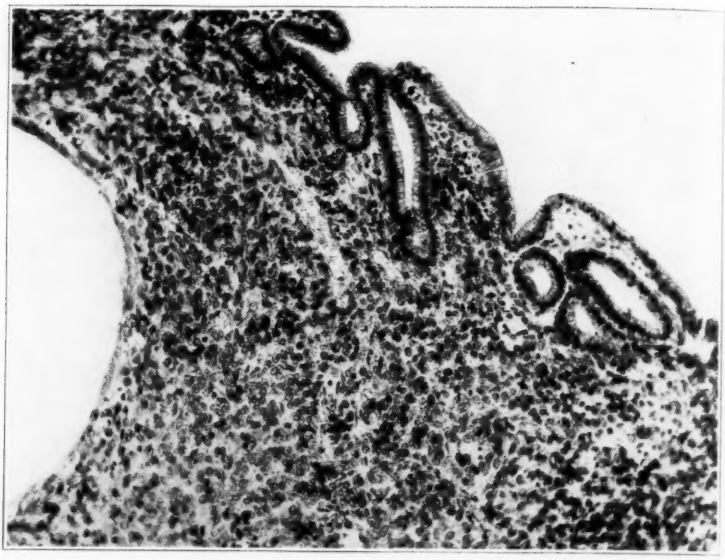


Fig. 9.—Lining membrane of the large tumor cyst. The single layer of epithelium produces short tubules lined by typical goblet cells. This section was taken from the margin of one of the smaller cysts. Its epithelial lining bears no resemblance to that of the larger cyst and was not mucus-producing; × 160.

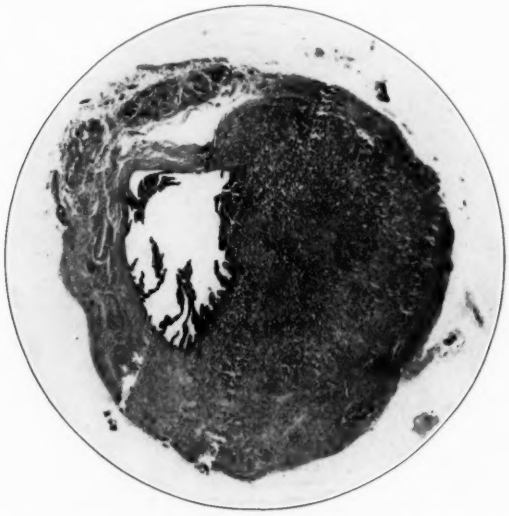


Fig. 10.—The tumor of rete tissue in the oviduct wall; × 10.

Attached to the outer half of the left tube by two threadlike cords was a firm, grayish-white hour-glass body, with a slightly furrowed surface, 4 cm. in length and 2.2 cm. in greatest diameter. It consisted largely of extremely dense acellular fibrous tissue. At its surface, however, was a layer of typical ovarian stroma in which were occasional corpora fibrotica. At its center was a narrow cleft lined with a wrinkled membrane colored a slight brownish yellow by many large cells laden with a brown iron-containing pigment. The other mass, described in the

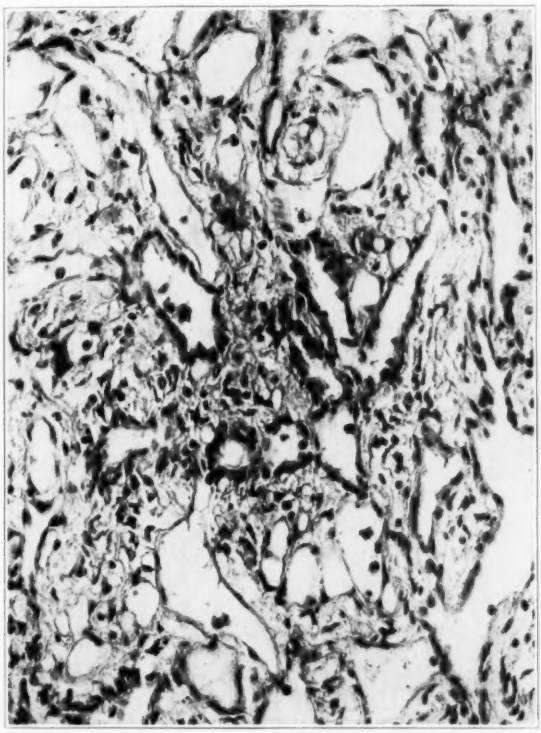


Fig. 11.—A high power magnification of rete tissue from the wall of the oviduct; × 300.

surgical report, attached to the one just described and to the ovary, was accidentally destroyed.

COMMENT

The secondary sexual characteristics of the woman, originally feminine, changed materially in the course of three years. They went beyond the commoner intersexual stage to one definitely masculine. Then, after removal of the tumor, the feminine characteristics returned to a partial degree, and after one year there has been no recurrence

of the tumor or return of the male characteristics. The mass was ovarian in origin, as shown by its location and by the ovarian stroma found on a part of its periphery. The return of feminine characteristics and particularly the continued normal menstruation after the operation are indicative of a normal function of the remaining gonadal tissue. There was no definite clinical evidence for incriminating any of the endocrine organs other than the ovary. It seems definite, then, that the tumor of the ovary was responsible for the changes noted.

The tumor consisted, probably, of testicular tissue. There was cord formation but no attempt at the construction of tubules or acini, nor was there any spermatogenesis. The chief cells were of two types. One was often noted in groups, with a relation to blood vessels suggestive of endocrine structures in general (figs. 6 and 7). This cell exhibited many of the structural characteristics of the testicular interstitial cell of Leydig, especially the peculiar distribution of fat (fig. 8) described by Wagner,[4] Whitehead[5] and Winiwarter.[6] It did not show the pigment common in the Leydig cell noted in man or the crystalloids of Reinke,[7] which may or may not be present in man. It did not suggest any other normal cell. The second type of cell was fusiform, suggestive of embryonic fibrous tissue, with some evidence of change into the former type. It may have represented the mesodermal tissue from which the interstitial cell is said to arise. If one accepts the contention that the Leydig cell elaborates the male hormone, the clinical course offers confirming evidence which warrants the assumption that these are testicular interstitial cells in varying degrees of development. The microscopic picture, on the whole, was highly suggestive of arrhenoblastoma as it has been described, and the clinical course was so typical that a diagnosis was made before operation. It seems probable, then, that the tumor from my patient falls into the group of arrhenoblastomas and consists chiefly of testicular interstitial cells.

It has been suggested that the arrhenoblastoma is but a special form of teratoma. Ewing[8] mentioned teratomas consisting entirely of thyroid tissue but did not mention such tumors containing gonadal structures. Such a classification would depend on finding in the tumor

4. Wagner, K.: Zur Zytologie der Zwischenzellen des Hodens, Anat. Anz. **56**:559, 1922.

5. Whitehead, R. H.: Chemical Nature of Certain Granules in the Interstitial Cells of the Testis, Am. J. Anat. **14**:63, 1912.

6. Winiwarter, H.: Observations cytologiques sur les cellules interstitielles du testicule humain, Anat. Anz. **41**:309, 1912.

7. Rasmussen, A. T.: Interstitial Cells of the Testis, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 2, sect. 35, p. 1909.

8. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

tissue that does not occur in the gonad of either male or female. My associates and I found such tissue; we have been able to demonstrate in the walls of a cyst in the tumor columnar, mucus-producing epithelium with typical goblet cells (fig. 9). The tissue was entirely quiescent and was taking no part in the active proliferation shown by the actual tumor cells. This structure, since it is foreign to ovary or testis, puts the tumor into the group of teratomas.

With regard to the question of recurrence, the number of mitotic figures and the cellularity of the tumor would ordinarily stamp it as malignant. However, it was well encapsulated everywhere except at the point of omental attachment. There is good physiologic evidence that the cells showed activity comparable to that of normal endocrine tissue. The Leydig cells have been thought to be holocrine, liberating their hormone only on disintegration, and it might be supposed that the cellular division, observed chiefly in the more immature fusiform elements, was only such as was necessary to provide for the replacement of the functioning cells. In this case the tumor may prove, in fact, to be benign.

Nothing was noted to indicate the cell type from which the tumor arose. Meyer [2] considered the ovarian medullary cords of Kölliker the probable origin of such a growth, but Fell [9] traced directly to the germinal peritoneum masculine tissue which had changed the sexual characteristics of a number of hens. It is significant, too, that other tissues of neighboring embryonic origin have the power of elaborating the male hormone under special circumstances, as is seen in the virilism accompanying tumors of the adrenal glands. In addition, it has been suggested that displaced bits of fetal tissue might be the source of the tumor. Such fetal rests often accompany various anomalies, and my patient gave evidence of developmental defects in the reproductive system, noted in the accessory ovarian tissue present in the mass attached to the left oviduct. Since the small nodule in the tubal wall was microscopically typical of rete testis (fig. 11), it seems probable that undifferentiated tissue was present in this location and that the tissue, under the stimulus of the male hormone from the tumor, developed in a masculine direction. It is not unlikely, therefore, that a similar group of fetal cells in the ovary, growing in response to an unknown stimulus, might well have been the source of the patient's tumor.

Precedent for the development of masculine tissue in females has been noted in sex reversal in lower animals, in a moth by Goldschmidt,[10]

9. Fell, H. B.: Histological Studies on the Gonads of the Fowl: I. The Histological Basis of Sex Reversal, Brit. J. Exper. Biol. **1**:97, 1923.

10. Goldschmidt, R.: Mechanismus und Physiologie der Geschlechtsbestimmung, Berlin, Gebrüder Borntraeger, 1920; quoted by Crew.[14b]

in fish by Essenberg,[11] in frogs by Witschi [12] and by Crew,[13] and in fowls by Crew [14] and by a group of other workers whose reports were summarized by Fell.[9] Crew [14] reported that the formation of a malignant tumor with a similar change in the sexual characteristics has occurred in hens, but I have been unable to find the original descriptions of the tumors. Greenwood and Blyth [15] reported active feminization of a capon due to a malignant tumor similar to the embryonic carcinoma of the human testis. All the reports, except those of the malignant tumors, told of more or less complete formation of a testis, which in some instances was functional.

The possible rôle of genetics in such phenomena is worthy of consideration. It is significant that in the cases of functional sexual reversal just described the ratio between the sexes in the offspring was such as to indicate that abnormal genetics played no part.

In conclusion, if one accepts as the diagnostic criterion for a teratoma that it contains tissue not found in the organ of origin or its homologs, it is proper to conclude that the ovarian tumor removed from my patient was of that group. Clinically the growth was identical, however, with the arrhenoblastomas, and pathologically it was highly suggestive at least of the more undifferentiated types of this tumor as they have been described. This suggests that the previously reported arrhenoblastomas may have been a special type of teratoma.

SUMMARY

A case of an ovarian tumor that falls into the group of twenty-nine previously reported cases of arrhenomastoma is reported.

The tumor consisted chiefly of testicular interstitial cells and embryonic mesodermal fibrous tissue but also contained tissue which is not found in the gonad of either sex.

The tumor is believed to be a special form of teratoma.

---

11. Essenberg, J. M.: Sex Differentiation in the Viviparous Teleost, Xiphorus Helleri. Biol. Bull. **45**:49, 1923; quoted by Crew.[14b]

12. Witschi, E.: Am. Naturalist **55**:529, 1921; quoted by Crew.[14b]

13. Crew, F. A. E.: A Description of Certain Abnormalities of the Reproductive System Found in Frogs and a Suggestion as to Their Possible Significance, Proc. Roy. Soc. Edinburgh **20**:236, 1921.

14. Crew, F. A. E.: (*a*) Studies in Intersexuality: II [Fowl], Proc. Roy. Soc., London, s.B **95**:256, 1923; (*b*) The Genetics of Sexuality in Animals, New York, The Macmillan Company, 1927.

15. Greenwood, A. W., and Blyth, J. S. S.: Reversal of the Secondary Sexual Characters in the Fowl: A Castrated Brown Leghorn Male Which Assumed Female Characters, J. Genetics **26**:199 (Oct.) 1932.

PROLIFERATIVE ENDOPHLEBITIS (PHLEBOSCLEROSIS)

REPORT OF A CASE

PAUL M. LEVIN, M.D.
AND
PAUL C. BUCY, M.D.
CHICAGO

Proliferation of the intima of the peripheral veins is a condition to which little attention has been directed in clinical medicine. The reason for this is readily understood when one reads in an eminent and authoritative system of internal medicine [1] that the disease (phlebosclerosis) produces no clinical symptoms. The few notes that appear in the literature deal mainly with a pathologic description of the lesions.

The term "phlebosclerosis," commonly used for this condition, suggests that the pathologic alteration in the veins is comparable to that seen in the arteries in arteriosclerosis. For this reason we prefer to call it "proliferative endophlebitis," although the condition does not appear to be inflammatory. "Proliferative endophlebosis" would perhaps be more accurate, since the term is noncommital as to etiology, but it does not sound well.

The purpose of this communication is to report a case in which there was presented a clinical syndrome of chronic partial venous obstruction with the pathologic finding of proliferative endophlebitis.

REPORT OF CASE

History.—Mrs. B. K. J., aged 24, was admitted to the University of Chicago Clinics on July 10, 1934, referred by Dr. W. J. Corcoran. She complained that she had pains in the muscles of the legs on standing and that the condition was of more than two years' duration. She stated that she had become pregnant for the first time in July 1931. Four months later she noticed a mottled discoloration of the feet, gradually extending to the kness. This condition appeared only when the legs were dependent, particularly when she stood. It was not associated with edema or evidence of thrombophlebitis. There was no toxemia of pregnancy. Labor, which occurred at term, and the postpartum period were normal.

One month after delivery the superficial veins of the legs seemed to swell, and she began to have dull aching pain in both calves. The pains gradually

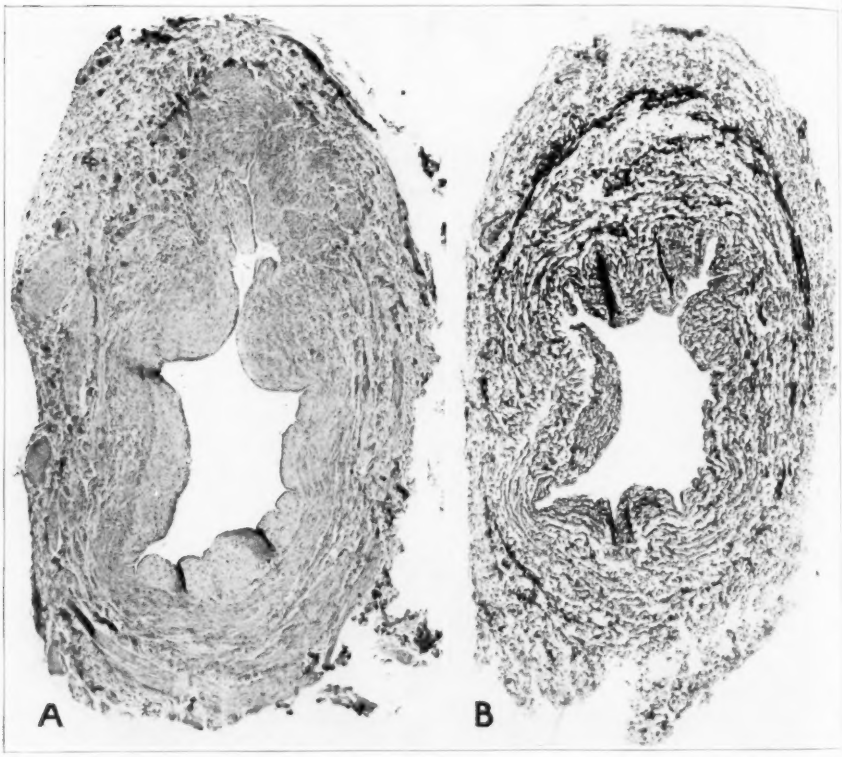
---

Presented before the Chicago Pathological Society on Feb. 11, 1935.

From the Division of Neurology and Neurosurgery of the University of Chicago Clinics.

1. Mohr, L., and Staehelin, R.: Handbuch der ineren Medizin, Berlin, Julius Springer, 1928.

increased and extended up the medial sides of the thigh to the groins. The discomfort appeared when she was standing, and it was relieved when she walked or lay down. The muscles of the calves seemed firm on palpation. At about this time the veins of the arms were affected similarly but to a lesser degree than those in the legs, with tenderness along the lateral sides of the arms, mottling of the skin and cyanosis of the fingers when dependent. The condition in the arms lasted only a short time, but that in the lower extremities was persistent. Examinations always failed to reveal varicose veins. Of the forms of treatment that were given,



A, photomicrograph of a transverse section of a vein showing marked thickening of the subendothelial layer and absence of inflammatory reaction (hematoxylin and eosin; × 34); *B*, photomicrograph of the same section showing abundant reticulin network (Laidlaw's silver impregnation; × 34).

contrast baths seemed to lessen the stiffness of the musculature of the calves, and elastic stockings gave considerable symptomatic relief.

At no time did intermittent claudication occur or attacks suggesting vascular spasm. Exposure to cold did not increase the symptoms; emotional stress occasionally seemed to aggravate the discomfort. There was never any edema of the extremities.

Moderate leukorrhea had been present since the pregnancy, but it decreased slightly after cauterization of the cervix. The past and family histories were not significant.

Examination.—The patient was well nourished and in excellent general health. The principal finding was tenderness of the superficial veins of the lower extremities, including the saphenous veins. Some of the smaller ones, especially those over the lower part of the tibia, were distinctly thickened, forming visible ridges beneath the skin. When the patient stood the feet and legs became cool, purplish and mottled. She then complained that there was aching of the feet and calves; this was relieved by massage or walking as well as by lying down. No blanching appeared when the legs were elevated. Trendelenburg's test was negative. The peripheral arteries were all soft and pulsated well. The pulse rate was 80 per minute. The blood pressure was 110 systolic and 68 diastolic in the brachial arteries and 140 systolic and 85 diastolic in the femoral arteries. Several small firm lymph nodes, not tender, were palpable in the inguinal regions and single ones in the axillae. Neurologic examination disclosed lively tendon reflexes and a bilateral Hoffmann sign but no Babinski sign; the palms were moist. The heart and other viscera were normal. Aside from slight leukorrhea, examination of the pelvis disclosed no abnormal condition.

Routine laboratory tests, including the Wassermann, were all negative.

The taking of temperatures of the skin over various parts of the body showed that the feet were 5 C. (9 F.) cooler than the rest of the body. Warming the upper extremities and the trunk did not influence the temperature of the feet. Under local anesthesia a small segment of a thickened vein over the lower part of the right tibia was removed for histologic examination. Following this procedure both feet curiously became warmer, their temperature equaling that of the rest of the body. The patient stated that this was the first time in two years that the feet had been definitely warm.

After discharge from the hospital, the patient wrote that the feet remained warm for one week. Then, one night, they became chilled, and the previous cool and mottled state returned.

Description of Vein.—The removed segment of a vein was narrow and white, and its walls were stiff. The lumen remained open. Microscopic preparations stained by various specific methods showed the great thickening of the wall (fig., *A*). This was due largely to an increase in the collagen affecting particularly the intima directly beneath the endothelium. In this region there was an abundant network of fine reticulin fibrils (fig., *B*). The intima varied considerably in thickness. The endothelium was for the most part normal, but in places the cells appeared swollen and more numerous. The other layers were less affected, the media showing perhaps moderate fibrosis and the adventitia little change. Sections stained for elastic tissue showed splitting of the intimal elastic fibers. There was no cellular infiltration, nor any evidence of previous thrombosis. Calcific or fatty change had not taken place.

Comment.—The symptoms which this patient presented indicate interference with the return of blood from the lower extremities. Discomfort was present when the parts were dependent and inactive; elevation of the extremities or muscular exercise alleviated the symptoms. The veins were palpably thickened and tender; on histologic examination they showed fibrotic proliferative changes, especially in the intima. The pathologic features disclosed are similar to those reported by

Stahl and Zeh [2] with the exception that their patient showed calcification of the intima. These authors presented a thorough review of the literature. More recently in this country Hauswirth and Eisenberg [3] discussed the condition, regarding it as much more common than hitherto considered. In their experience the lesions do not cause clinical disturbance of circulatory function.

SUMMARY

A case of proliferative endophlebitis is presented which appears to be unique in that the lesions were associated with symptoms definitely indicative of impairment of the venous return.

2. Stahl, R., and Zeh, F.: Ueber Sklerose der peripheren Venen, Virchows Arch. f. path. Anat. **242**:70, 1923.

3. Hauswirth, L., and Eisenberg, A. A.: Disseminated Venofibrosis (Phlebosclerosis), Arch. Path. **11**:857 (June) 1931.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SOME CONTRIBUTIONS MADE DURING 1935

ASHTON GRAYBIEL, M.D.
AND
PAUL D. WHITE, M.D.
BOSTON

The number of papers relating to heart disease published during 1935 was amazingly large. Obviously only a few can be reviewed. As it is, we have been insensibly led to greater length than was first planned. The material has been organized very simply with the view of better correlating the various aspects of a particular problem or disease.

PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY

Some of the reports which might properly be placed under this heading are discussed appropriately in other sections.

Rytand and Dock [1] have made an interesting study of cardiac hypertrophy. Renal insufficiency was produced in one group of rats, and the hypertrophied hearts were compared with the hearts of rats fed desiccated thyroid and with the hearts of normal controls.

The authors found that the heart of the rat made hypertensive by deprivation of renal tissue reacts by an increase in the weight of its left ventricle alone, while the cavity of the left ventricle not only does not dilate but is relatively small in comparison with the weight of its surrounding myocardium. In the concentric hypertrophy so induced, the myocardial fibers of the left ventricle are increased in width and decreased in length. The heart of the rat fed thyroid extract becomes heavier in both ventricles equally, while the dilatation of the left ventricle closely parallels hypertrophy. In the eccentric hypertrophy so induced the myocardial fibers do not show a significant change in width, but they lengthen greatly. From a consideration of cardiodynamics it is shown that concentric hypertrophy is the optimum compensatory mechanism for the hypertensive heart, which must expel a normal minute output against an increased peripheral resistance in the systemic

From the Cardiac Clinic of the Massachusetts General Hospital.

1. Rytand, David A., and Dock, W.: Experimental Concentric and Eccentric Cardiac Hypertrophy in Rats, Arch. Int. Med. **56**:511 (Sept.) 1935.

circuit, while eccentric hypertrophy is the optimum compensatory mechanism for the heart which must expel an increased minute output against presumably normal peripheral resistance.

Evans, Grande and Hsu [2] have shown that the working heart, in contrast to skeletal muscle, shows the ability to utilize lactic acid derived from the blood and that the rate of such utilization is roughly proportional to the amount of work done and the concentration of lactic acid in the perfusing blood. It was shown furthermore [3] that if the heart is made to utilize more lactic acid by the addition of sodium lactate to the perfusing blood, increase of the coronary flow, decrease of heart rate and lowering of venous pressure can be observed. Control experiments were performed with sugar and sodium bicarbonate in similar concentration, but the beneficial effect was not usually observed. Bogue, Evans and Hsu expressed the opinion that it is therefore highly probable that the effect is specific to the lactate ion. They stated that in the resting state of the intact body the lactate content of the blood is at its basic level and consequently its usage by the heart is small. During strenuous muscular exertion, however, the lactate content of the blood is enormously increased, and at the same time the heart is required to do more work. It is under these conditions that the ability of the heart to utilize lactic acid shows its full significance. Not only does lactic acid promote contractility of the cardiac muscle, but, like carbon dioxide, it tends to slow the rate and increase the efficiency. Since the rate at which the lactic acid penetrates into the cardiac tissues is greater than that at which sugar is absorbed, lactic acid is more readily available to meet the increased demands for fuel by the heart. Moreover, the rate of utilization is facilitated by the property of lactic acid itself to increase the coronary flow.

Harris, Jones and Aldred [4] have found that under resting conditions the lactic acid content of the blood is increased in cases of cardiac failure and that this increase stands in a definite relation to the degree of failure. The increase in lactic acid content after a standard exercise is greater the greater the degree of cardiac failure. They express the opinion that the accumulation of lactic acid in the blood in cases of heart disease is probably due to defective oxygenation but may be due to accumulation of carbon dioxide in the tissue of the respiratory center, which brings about alkalosis and an associated rise in the lactic acid

2. Evans, C. L.; Grande, F., and Hsu, F. Y.: Glucose and Lactate Consumption of Dog's Heart, Quart. J. Exper. Physiol. **24**:347, 1935.

3. Bogue, J. Y.; Evans, C. L., and Hsu, F. Y.: The Significance of Lactic Acid Uptake by the Mammalian Heart, J. Physiol. **84**:55P, 1935.

4. Harris, I.; Jones, E. W., and Aldred, C. N.: Blood p_H and Lactic Acid in Different Types of Heart Disease, Quart. J. Med. **4**:407, 1935.

content of the blood. Except in extremely severe conditions the p_H of the blood is normal in the different types of heart disease.

Weiss and Ellis [5] compared the utilization of oxygen and the production of lactic acid in the upper and lower extremities in normal subjects and in patients having heart disease with and without congestive failure. During rest, the average oxygen utilization was essentially the same in the arm and in the leg, and the values were similar for normal persons and for patients with heart disease without congestion. When congestive failure was present there was an increased peripheral utilization of oxygen, which is evidence that the blood flow through the extremities was reduced. On standing, the oxygen utilization of the extremities increased in all groups, as a result, in part at least, of a decrease in blood flow; immediately after exercise the oxygen utilization increased markedly. The average level of the lactic acid in the extremities during rest was between 12 and 14 mg. per hundred cubic centimeters for all groups; this does not agree with the results of others, who found an increased concentration of the lactic acid of the blood in patients with severe circulatory failure. Immediately after exercise the lactic acid content of the blood of the femoral vein draining the active muscle more than doubled; it then fell rapidly during the next ten minutes and more slowly in the succeeding ten minutes, but it did not reach the level observed during rest within twenty minutes. The lactic acid content of the venous blood of the inactive arm rose slightly immediately after the exercise, but in ten minutes it was similar to that of the leg, as a result of the mixing effect of the circulation. With the increasing severity of circulatory failure, there was a tendency for the lactic acid content of the blood of the femoral vein to rise to a higher level than normal immediately after exercise and to fall more slowly.

Weiss and Ellis commented on their observations as follows:

> As a result of these studies we consider that there is no evidence of a primary disturbance of the peripheral circulation as the precipitating factor in heart failure. There is evidence, however, that the peripheral circulation does not play a purely passive rôle, as was once widely believed. In normal persons, the cardiovascular functions can be increased efficiently and a certain amount of the load removed from the heart itself by peripheral vascular reflexes which tend to shunt blood where it is most needed and under greater pressure, particularly by increased oxygen utilization. The same factors, to a greater degree, tend to operate in patients with heart disease, with and without evidence of failure. With the aid of the peripheral circulation, compensation for an inadequate cardiac function may be achieved.

5. Weiss, Soma, and Ellis, Laurence, B.: Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise in Subjects with Normal and in Those with Diseased Cardiovascular Systems, Arch. Int. Med. **55**:665 (April) 1935.

ELECTROCARDIOGRAPHY

Dale [6] briefly referred to the many attempts made in the past to correlate the different phases of the electrocardiogram with other events in the cardiac cycle, such as the contraction process or the production of lactic acid. Since the discovery that the production of lactic acid in both cardiac and skeletal muscle is abolished by poisoning with iodoacetic acid, it has been possible to determine whether there is a correlation between any phase of the electrocardiogram and the formation of lactic acid. The frog's ventricle perfused with thoroughly aerated Ringer's solution has been shown to derive its energy from at least two sources, of which one is carbohydrate and the other, for want of more precise knowledge of its nature, may be termed noncarbohydrate. If oxygen is withheld from the perfusing solution, the frog's ventricle derives its energy solely from carbohydrate and contracts normally provided the perfusion medium is alkaline, thus allowing the muscle to excrete the lactic acid formed. On the other hand, a ventricle in which carbohydrate metabolism has been excluded by poisoning with iodoacetic acid can contract normally provided the perfusion solution is thoroughly oxygenated. It is possible, therefore, by subjecting a ventricle to the appropriate conditions to cause it to derive its energy from normal mixed carbohydrate and noncarbohydrate, pure carbohydrate and pure noncarbohydrate. Experiments were carried out to determine whether the type of metabolism has any influence on the electrical response. The change from mixed metabolism to pure carbohydrate metabolism produced a definite though slight effect on the mechanical and electrical responses, diminishing the former and increasing the duration of the latter, while the change to pure noncarbohydrate metabolism produced no definite effect. Dale concluded that it is possible to abolish the production of lactic acid in the frog's ventricle without affecting the duration or form of the electrical response.

Kountz and his co-workers [7] have made important and interesting electrocardiographic studies on revived perfused human hearts. Immediately after death the chest was opened, the pericardium incised and the heart perfused. In most cases the cardiac nerves were cut. Of a

6. Dale, A. S.: The Relation Between Metabolic Processes and the Ventricular Electrogram, J. Physiol. **84**:433, 1935.

7. Kountz, W. B.; Prinzmetal, M.; Pearson, E. F., and Koenig, K. F.: The Effect of Position of the Heart on the Electrocardiogram: I. The Electrocardiogram in Revived Perfused Human Hearts in Normal Position, Am. Heart J. **10**: 605, 1935. Kountz, W. B.; Prinzmetal, M., and Smith, J. R.: The Effect of Position of the Heart on the Electrocardiogram: II. Observations upon the Electrocardiogram Obtained from a Dog's Heart Placed in the Human Pericardial Cavity, ibid. **10**:614, 1935; III. Observations upon the Electrocardiogram in the Monkey, ibid. **10**:623, 1935.

total of 37 cases studied by this method, normal-appearing electrocardiograms were obtained in 8, and these were further investigated. Four general types of extrasystoles were observed. Discordant curves in which the initial ventricular deflection was up in lead I and down in lead III were obtained by stimulating the right ventricle everywhere except at the conus, where stimulation produced concordant extrasystoles in which the initial ventricular deflection was upright in all three leads. Discordant curves in which the initial deflection was down in lead I and up in lead III were obtained from the left ventricle except at the apex, where stimulation produced concordant extrasystoles in which the initial ventricular deflection was down in all three leads. When the right bundle branch was cut with the heart in the normal position, the initial ventricular deflection of the electrocardiogram was usually down in lead I and up in lead III; when the left bundle branch was cut, the initial ventricular deflection of the electrocardiogram was up in lead I and down in lead III. Shift of the heart to the right caused left axis deviation (present terminology) in the electrocardiogram, and shift to the left, right axis deviation. Rotation of the heart clockwise caused right axis deviation, while rotation counter clockwise caused left axis deviation.

Observations on the electrocardiograms obtained from a dog's heart placed in the human pericardial cavity and from the hearts of monkeys were in agreement with the observations just described.

The results reported by Kountz and his co-workers confirm the correctness of the newer terminology for bundle branch block and the recent opinion that what have been considered right ventricular extrasystoles are in reality left ventricular extrasystoles, and vice versa. Furthermore, the effect of shifting the heart confirms the view that what has been considered right axis deviation is in reality left axis deviation, and vice versa.

Mahaim,[8] however, on the basis of careful histologic studies on the bundle of His and its branches, expressed the belief that the old classic terminology in regard to bundle branch block is correct.

There have been many reports[9] concerning the electrocardiogram in cases of myocardial infarction; only a few are mentioned. They

8. Mahaim, Ivan: Nouvelles recherches sur les lésions du faisceau de His-Tawara. Le bloc de branche gauche et sa pathogénie. La septite mitrale, Ann. de méd. **38**:185, 1935.

9. Sprague, H. B., and Orgain, E. S.: Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital, 1914-1934, New England J. Med. **212**:903, 1935. Barnes, Arlie R.: Electrocardiogram in Myocardial Infarction: Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, Arch. Int. Med. **55**:457 (March) 1935. Jervell, A.: Elektrokardiographische Befunde bei Herzinfarkt,

(Footnote continued on next page)

contain the latest knowledge concerning this important branch of electrocardiography.

The precordial electrocardiographic "lead" appears to have a definite value, although to what degree it may complement the usual three leads is not yet fully established.

It seems wise to advise for routine examinations the use of a single chest lead, with the precordium at the cardiac apex the site of application for one electrode and the left leg for the other. It is well to label this lead as lead IV, disregarding for the present at least the complication of other chest leads, leads V to IX, inclusive. It has not been shown that chest leads other than lead IV are of significant practical value.

We agree with Roth [10] that many reports concerning lead IV "appear to be colored by an unwarranted enthusiasm on the subject, leading on the one hand to an overemphasis of the value of chest leads, and on the other to a tendency to underrate the significance of abnormalities in the standard leads." A considerably longer time and much more work are needed before the full and correct evaluation of lead IV can be made.

During 1935 several publications have appeared, some [11] of which may be referred to for a summary of the knowledge on lead IV to date, especially in regard to its value in the diagnosis of heart disease with involvement of the coronary arteries.

The use of chest leads as well as limb leads has enabled Wolferth and Wood [12] to predict correctly the site of the infarct in each of their twenty cases of acute coronary occlusion in which autopsy was performed during the past three years. They pointed to several factors which may confuse the observer in attempting to locate the lesion and

---

Acta med. Scandinav., supp. 68, 1935, p. 1. Johnston, F. D.; Hill, I. G. W., and Wilson, Frank N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: II., Am. Heart J. **10**:889, 1935. Wilson, Frank N.; Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: III., ibid. **10**:903, 1935. Wilson, Frank N.; Johnston, F. D., and Hill, I. G. W.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: IV., ibid. **10**:1025, 1935.

10. Roth, I. R.: On the Use of Chest Leads in Clinical Electrocardiography, Am. Heart J. **10**:798, 1935.

11. Faulkner, James M.: The Electrocardiographic Diagnosis of Acute Cardiac Infarction with Special Reference to the Value of Precordial Leads, New England J. Med. **213**:1215, 1935. Bohning, A., and Katz, L. N.: The Four Lead Electrocardiogram in Coronary Sclerosis: A Study of a Series of Consecutive Patients, Am. J. M. Sc. **189**:833, 1935. Roth.[10]

12. Wolferth, C. C., and Wood, F. C.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle, Arch. Int. Med. **55**:77 (July) 1935.

reported a group of ten cases in which there were electrocardiographic indications of acute lesions in both the anterior and the posterior wall of the left ventricle. In some cases the tracings suggested that the main lesion was anterior, and in others, that the main infarct was posterior. The most helpful signs were certain changes in the RS-T interval and in the QRS complex. In two of the ten cases necropsy was performed, revealing in each instance lesions involving part of both the anterior and the posterior wall of the left ventricle.

In following the effect of the rheumatic process on the heart with the aid of serial electrocardiography, Levy and Bruenn [13] found that the additional use of lead IV in certain instances revealed evidence of active carditis when in the usual three leads either no changes in form were apparent or the alterations noted were regarded as equivocal. About the only abnormalities noted in lead IV were variations in the form and amplitude of the T wave. Because of the variability of the T wave in lead IV, Levy and Bruenn pointed out that only changes in its form occurring in records taken on the same patient at different times may be regarded as evidence indicating alterations in the state of the myocardium. They stated, however, that such successive changes, while showing that the heart is affected and that the lesions are not in a quiescent state, are not specific indications of rheumatic fever.

Strauss and Katz [14] have studied the effect of digitalis on the appearance of lead IV. Seven normal persons were digitalized to the point of toxicity, and the appearance of the four lead electrocardiograms after medication was compared with that of the tracings made before digitalization was begun. The authors also studied six patients with various types of cardiac lesions in whom digitalization was demonstrable clinically and in the three usual electrocardiographic leads. The chief changes observed in lead IV were in the ST segment and the T wave, and these were reversible when the administration of digitalis was discontinued. In several instances the contour of lead IV closely resembled that seen after recent coronary occlusion, and Strauss and Katz emphasized the need of caution in interpreting these records.

Among a number of electrocardiographic clinical studies,[15] that of Schwab and Herrmann on alterations of the electrocardiogram in dis-

13. Levy, R. L., and Bruenn, H. G.: Precordial Lead of Electrocardiogram (Lead IV) as an Aid in Recognition of Active Carditis in Rheumatic Fever, Am. Heart J. **10**:881, 1935.

14. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, Am. Heart J. **10**:546, 1935.

15. Schwab, Edward H., and Herrmann, George: Alterations of the Electrocardiogram in Diseases of the Pericardium, Arch. Int. Med. **55**:917 (June) 1935. Rykert, H. E., and Hepburn, J.: Electrocardiographic Abnormalities Character-

(Footnote continued on next page)

ease of the pericardium is of considerable interest. They completely reviewed the medical literature on this subject and reported in detail 7 cases of pericardial disease of various types, including serial electrocardiographic studies. The chief electrocardiographic alterations were found to be a decrease in the voltage of the QRS complex, deviation of the RS-T segment from the iso-electric level and variations in the form and amplitude of the T wave. An evaluation of the electrocardiographic differences between pericardial disease and cardiac infarction is presented, and the absence of significant abnormalities of the Q wave in cases of pericardial pathologic processes is stressed. No information of differential value was derived from the use of lead IV.

New and simple methods [16] of avoiding high resistance and overshooting in taking standardized electrocardiograms have been described. The procedure involves the use of pastes which easily reduce cutaneous resistance below 2,000 ohms and form a nonpolarizing contact between the skin and the electrode.

ROENTGENOLOGY

Few articles concerning roentgen examination of the heart and aorta have been published during 1935. There is continued interest in kymography,[17] especially in Europe, but there have been no recent important contributions.

Warfield [18] wrote an interesting paper on the roentgen diagnosis of aneurysms of the innominate artery, stressing particularly methods of differential diagnosis from other tumors in the mediastinum and the necessity of first demonstrating the presence of aortitis.

---

istic of Certain Cases of Hypertension, Am. Heart J. **10**:942, 1935. Graybiel, Ashton, and White, Paul D.: Inversion of the T-Wave in Leads I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia, ibid. **10**:345, 1935. Aschenbrenner, R., and Bamberger, P.: Elektrokardiographische Untersuchungen an spasmophilen Kindern, Klin. Wchnschr. **14**:1494, 1935.

16. Jenks, James L., Jr., and Graybiel, Ashton: A New and Simple Method of Avoiding High Resistance and Over-Shooting in Taking Standardized Electrocardiograms, Am. Heart J. **10**:693, 1935. Russell, H. B.: The Use of Cambridge Electrode Jelly, Lancet **2**:1173, 1935.

17. Kahlstorf, A., and Ohnesarge, E.: Die diagnostische Bedeutung der pulsatorischen Aortenbewegungen im Flächenkymogramm, Fortschr. a. d. Geb. d. Röntgentrahlen **51**:22, 1935. Holst, L.; Klioner, I.; Koppelmann, S., and Speranskij, N.: Die Flächenkymographie des Herzens, ibid. **51**:454, 1935. Klioner, I., and Ivanov, N.: Die normale Herzkurve und die physiologischen Veränderungen derselben im Flächenkymogramm, ibid. **51**:469, 1935.

18. Warfield, C. H.: Roentgen Diagnosis of Aneurysms of the Innominate Artery, Am. J. Roentgenol. **33**:350, 1935.

Brown and McCarthy [19] studied the abnormal conditions which affect the position of the esophagus. While the material presented is not new, it is well discussed.

Parade [20] called attention to 2 cases of mitral stenosis in which roentgen therapy was followed by auricular fibrillation. In 1 instance the heart was directly exposed to the rays; in the other it was not. Parade suggested that substances liberated in the course of the roentgenotherapy exert a harmful effect on the heart or its regulatory mechanism. The experiments of Nahum and Hoff [21] may be remembered with interest in this connection.

Udvardy [22] found no uniform configuration of the heart in cases of emphysema, for in the various stages of this disorder the heart undergoes various changes. At first the size of the heart is reduced because the thorax is fixed in inspiration and the intrapulmonary pressure is raised; the entire picture, the lungs as well as the heart, are seen as in Valsalva's experiment. With the progress of the disease, the right ventricle gradually becomes larger, and finally the entire heart enlarges to such a size that a "mitral configuration" is suggested, especially as the pulmonary arc is prominent.

HEART SOUNDS AND MURMURS

A large number of papers [23] have appeared on heart murmurs and sounds, including gallop rhythm. Nothing new of great clinical sig-

19. Brown, S., and McCarthy, J. E.: Study of the Esophagus in Relation to the Heart, Aorta and Thoracic Cage, Radiology **24**:131, 1935.

20. Parade, G. W.: Herzschädigung bei Röntgenbestrahlung, Med. Klin. **31**: 1396, 1935.

21. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methylcholine Chloride, with Observations on the Rôle of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, J. A. M. A. **105**:254 (July 27) 1935.

22. Udvardy, L.: Form- und Grössenveränderungen des Herzens bei Erkrankungen der Lungen, Pulmonalsklerose, Fortschr. a. d. Geb. d. Röntgenstrahlen **52**: 115, 1935.

23. Duchosal, P.: Nouvelles recherches graphiques sur le bruit de galop, Arch. d. mal. du cœur **28**:345, 1935. Wolferth, Charles C., and Margolies, Alexander: Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sound, Am. Heart J. **10**:425, 1935; The Influence of Varying As-Vs Intervals on Split First Heart Sounds: Its Bearing on the Cause of Split Sounds and the Mechanism of the First Sound, J. Clin. Investigation **14**:605, 1935. Thompson, W. P., and Levine, S. A.: Systolic Gallop Rhythm: Clinical Study, New England J. Med. **213**:1021, 1935. Friedlander, R. D., and Brown, M. G.: The Systolic Murmur: Further Observations on Its Clinical Significance, Ann. Int. Med. **8**:893, 1935. Bramwell, Crighton: Sounds and Murmurs Produced by Auricular Systole, Quart.

(Footnote continued on next page)

nificance is reported, and owing to considerations of space the papers are not reviewed.

CONGENITAL HEART DISEASE

No contribution of great importance has been presented under this heading, although many interesting cases have been reported.

RHEUMATIC HEART DISEASE

Inquiry into the cause of rheumatic fever has been given direction, largely, by the fact that tonsillitis or pharyngitis frequently precedes the rheumatic process. Naturally, organisms responsible for infections of the upper portion of the respiratory tract have been studied exhaustively. The rarity of the finding of bacteria in rheumatic inflammatory lesions, however, led to the suggestion that these lesions may be allergic. This supposition has gained support chiefly on histopathologic grounds and on the basis of the clinical fact that a "silent" or "latent" period intervenes, usually, between the rheumatic attack and the preceding infection of the respiratory tract.

During the past few years interest has centered chiefly on the hemolytic streptococci, and great efforts have been made to establish a constant relationship between a focus of streptococcic infection and rheumatic fever. Cultural methods have been supplanted largely by the more delicate and indirect immunologic reactions. These include the precipitation, agglutination and complement-fixation reactions and the determination of antihemolysins, antistreptolysins and antifibrolysins. In the past year a number of reports [24] have appeared concerning one or another of the aforementioned procedures. Although the results of different workers are not in agreement, evidence shows that there is often a relationship between the development and intensity of the immune

---

J. Med. **4**:139, 1935; Gallop Rhythm, ibid. **4**:149, 1935. de Chatel, A.: Veränderungen des ersten Herztones bei Ueberleitungsstörungen, Klin. Wchnschr. **14**: 1004, 1935. Bierring, Walter L.; Bone, H. C., and Lockhart, M. L.: Use of the Electrostethograph for Recording Heart Sounds, J. A. M. A. **104**:628 (Feb. 23) 1935. Routier, Daniel, and Van Heerswynghels, J.: A propos du bruit de galop. Etude phonocardiographique, Arch. d. mal. du cœur **28**:629, 1935.

24. Beck, A., and Coste, F.: Streptococcus Complement-Fixation Reaction in Rheumatic Diseases, Brit. J. Exper. Path. **16**:20, 1935. Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process: I, II and III, J. Exper. Med. **62**:129, 137 and 159, 1935; IV, V and VI, J. Clin. Investigation **14**:755, 763 and 769, 1935. Schlesinger, B.; Signy, A. G., and Payne, W. W.: Further Studies on the Aetiology of Acute Rheumatism, Lancet **1**:1090, 1935. Wilson, May G.; Wheeler, George W., and Leask, Marguerite M.: The Relation of Upper Respiratory Infections to Rheumatic Fever in Children: II. Antihemolysin Titres in Respiratory Infections and Their Significance in Rheumatic Fever in Children, J. Clin. Investigation **14**:333, 1935.

response to hemolytic streptococci and those of acute rheumatism. However, there are frequent exceptions to this close relationship, and some of these will now be considered.

Occasional instances of reactivation of rheumatic fever by events other than streptococcic infection have attracted the attention of Bland and Jones.[25] Transient and unexplained elevations of temperature, accidents, operations and various infections were found to have a relationship to relapses in cases of rheumatic fever similar to that of streptococcic infection. Especially interesting was the case of a girl with severe chorea and minimal rheumatic heart disease, in whom a rectal temperature of 108.9 F. developed after the third daily injection of stock typhoid-paratyphoid vaccine. The chorea became less severe, but reactivation of the rheumatic fever occurred two weeks later. Stimulated by this observation, Bland and Jones selected 10 young persons for further study. All were in excellent general physical condition but exhibited evidence, chiefly from laboratory examination, of low grade chronic rheumatic fever. These 10 patients received twelve intravenous injections of 0.1 cc. of typhoid-paratyphoid vaccine, which caused a slight febrile reaction and chill. In 6 instances clinical and laboratory evidence of reactivation of rheumatic fever appeared either immediately after the injection or two or three weeks later. In 4 instances there was no evidence, and in 2 there was slight evidence, of reactivation. These artificially provoked recurrences were mild and led to no significant injury but "reproduced in a striking fashion the rheumatic manifestations which had been previously observed in the individual patient during a naturally occurring recrudescence." These observations led Bland and Jones to conclude that the rôle of infections or other episodes apparently related to the rheumatic process should be regarded as nonspecific.

That rheumatic fever may be due to a factor which becomes operative when some predisposing event places the body in a vulnerable state is a commonly held supposition. Important evidence that this factor may be a virus has been advanced by Schlesinger, Signy, Amies and Barnard.[26] They employed methods similar to those used successfully in the identification of the viruses of vaccinia and psittacosis. Pericardial and pleural fluids from patients dying of active rheumatic infection were submitted to centrifugation at high speed. The deposits, shown

25. Bland, Edward F., and Jones, T. Duckett: Clinical Observations on the Events Preceding the Appearance of Rheumatic Fever, J. Clin. Investigation **14**: 633, 1935.

26. Schlesinger, B.; Signy, A. G.; Amies, C. R., and Barnard, J. E.: Aetiology of Acute Rheumatism: Experimental Evidence of a Virus as the Causal Agent, Lancet **1**:1145, 1935.

to be sterile by cultural methods, were examined microscopically by dark-field and tinctorial methods as well as according to Barnard's special technic. Particles of uniform character were seen which resembled the elementary bodies observed in diseases known to be caused by a virus. Pericardial fluid from 7 patients was examined in this fashion, and elementary bodies were seen in 6 instances; fluid in which similar bodies were not found came from a patient with a chronic rheumatic infection. Elementary bodies were found in the deposit obtained from the pleural exudate of 1 patient with rheumatic pneumonia. Control fluids failed to show these virus-like particles.

This matter was carried a step further by showing that these elementary bodies are specifically agglutinated by the serums of patients who are suffering from, and successfully resisting, an acute rheumatic infection. Serum of patients with quiescent rheumatism failed to agglutinate these bodies.

The authors made the following suggestions:

> . . . the bodies found in the pericardial exudates represent the actual infective agent of acute rheumatism.
>
> The importance of streptococcal infection as a factor in the etiology of the disease is recognized. It is suggested that the lowered resistance produced by such infections enables the virus to enter the body or, if the virus is already lying latent in the tissues, allows it to assume active characters.

Coles [27] claimed to have seen these virus bodies in the pericardial exudate obtained from patients dying not only of rheumatic fever but of various other causes, including accidents, sepsis and malignant leukemia.

The findings of Schlesinger and his co-workers [26] are suggestive despite their incompleteness and are not open to facile criticism. Much remains to be done, and already there are attempts to reproduce rheumatic fever in animals known to be susceptible to certain diseases caused by a virus.

Numerous pathologic studies have emphasized the causal relationship between rheumatic fever and vascular injury. Lesions have been described in all orders of vessels from aorta to capillaries. For the greater part these lesions are not considered specific of rheumatic fever, although Aschoff nodules have been described as occurring in several parts of the vascular tree.

The development of nodular lesions in the ascending portion of the aorta during rheumatic fever is well known since the work of Pappenheimer and Von Glahn, Klotz and others. Gross [28] has described the

27. Coles, A. C.: Virus Bodies in the Pericardial Fluid of Rheumatic Fever, Lancet **2**:125, 1935.

28. Gross, L.: Lesions in Roots of Pulmonary Artery and Aorta in Rheumatic Fever, Am. J. Path. **11**:631, 1935.

lesions found in the roots of the pulmonary artery and aorta, together with their pericardial mantles, in 150 hearts. Sixty-six hearts were from patients with active rheumatic fever, 34 from patients with inactive disease and 50 from normal control persons. In all the patients with active rheumatic disease there was either microscopic pericarditis or acute exudative pericarditis in relation to the roots of the great vessels, which may have accounted for the high incidence of their capillarization (capillarization occurred in over 70 per cent of the patients with inactive as well as active disease and in only 25 per cent of the controls). In patients with active rheumatic fever the incidence of inflammatory and destructive lesions in the pulmonary roots was nearly as high as that of lesions in the aortic roots, although scarring was more conspicuous in the latter. Some of the lesions were similar to those occurring in nonrheumatic controls owing to changes resulting from age, while others were more characteristic. The lower incidence of the more characteristic lesions in the group of patients with inactive disease indicates that healing may sometimes occur.

Gigante,[29] working in Aschoff's laboratory, carefully studied the abdominal aorta and carotid arteries from 30 rheumatic and nonrheumatic patients. He failed to find either Aschoff nodules or specific types of scarring which might have resulted from previous rheumatic involvement. His findings, consequently, are not in accord with those of Klinge, who has described specific rheumatic lesions in the abdominal aorta which, in his opinion, are associated with the development of atherosclerosis.

Gross, Kugel and Epstein [30] have described, classified and compiled statistics on the vascular lesions in the coronary arteries as they occur in cases of active and inactive rheumatic fever. Their conclusions are in general agreement with previous studies in this field. They emphasized the marked vascular damage found in the cases of active disease, which "may be so extensive that it would be difficult if not hazardous to venture an opinion as to whether the vascular or primary myocardial injury is the more significant with regard to the life of the patient." Vascular lesions in the cases of inactive disease were essentially similar to those found in control hearts, but their development was precocious. In the experience of the present authors, however, important disease of the coronary arteries in youth has been found rarely in association with evident rheumatic heart disease or with a past history of rheumatic infection.

29. Gigante, D.: Ueber die Atherose und Atherosklerose der Bauchaorta, der Carotiden und der Sinus carotici, und ihre Beziehungen zum Rheumatismus specificus infectiosus, Beitr. z. path. Anat. u. z. allg. Path. **95**:71, 1935.

30. Gross, Louis, Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, Am. J. Path. **11**:253, 1935.

Auricular lesions in cases of rheumatic fever have been widely recognized since the publication of studies by MacCallum, Thayer, Von Glahn and others. Gross [31] has examined the left auricle in 87 rheumatic hearts and classified the material into five clinical groups according to the stage of the disease. Of especial interest was the finding of macroscopic lesions in 80 per cent of the cases and of microscopic lesions in 100 per cent. In about 50 per cent of the cases there was microscopic evidence of some lesion in the pericardium overlying the left auricle.

Bland, White and Jones [32] have presented clinical and postmortem observations on a group of 100 young patients with rheumatic heart disease with especial regard to the development of deformity of the mitral valve, and the interpretation of mitral diastolic murmurs. It was found that a period of at least two years from the onset of rheumatic fever was necessary for the development of extensive valvular deformity either with or without stenosis. Of 47 patients who died two years or more after the onset of rheumatic fever, only 20 had frank mitral stenosis. Sixty-eight of the 100 patients had a rumbling mitral diastolic murmur, accompanied by a thrill in 30 instances, which led to a clinical diagnosis of mitral stenosis. Of these 68, only 21 had anatomic stenosis of the mitral orifice, 19 had gross deformity of the cusps without stenosis and the remaining 28 had either no deformity or, at most, minimal thickening of the free margin of the valve. Of these last 28 patients only 2 had aortic regurgitation to a sufficient degree to require consideration of an Austin Flint murmur. Myocardial weakness and ventricular dilatation occurring during the course of active rheumatic fever appeared to be responsible for the production of the mitral diastolic murmur in these patients.

In a group of patients with acute rheumatic heart disease studied clinically, the mitral systolic and diastolic murmurs were found to disappear in a number of instances after the subsidence of the active infection. This clears up the mystery of such an event, the significance of which has been variously interpreted in the past—for example, by the assumption that valvular disease retrogressed or became clinically unrecognizable.

De Graff and Lingg [33] have studied carefully the course of rheumatic heart disease in 644 fatal cases in a total of 1,633 cases coming

31. Gross, Louis: Lesions of the Left Auricle in Rheumatic Fever, Am. J. Path. **11**:711, 1935.

32. Bland, Edward F.; White, Paul D., and Jones, T. Duckett: The Development of Mitral Stenosis in Young People with a Discussion of the Frequent Misinterpretation of a Middiastolic Murmur at the Cardiac Apex, Am. Heart J. **10**: 995, 1935.

33. De Graff, Arthur C., and Lingg, Claire: The Course of Rheumatic Heart Disease in Adults: I, II and III, Am. Heart J. **10**:459 and 630, 1935.

under observation. Of these 644, 55.8 per cent were in male and 44.2 per cent in female patients. De Graff and Lingg found that this disease runs its course chiefly within the first four decades. The average age at the initial infection was found to be 17 years; that at the first symptom of cardiac insufficiency, 28 years; that at the first appearance of heart failure,[34] 30 years, and that at death, 33 years. Mitral valvular disease was found to be more frequent in women, whereas aortic disease was approximately twice as frequent in men. Lesions of the tricuspid or the pulmonary valve were comparatively rare. Valvular disease in itself afforded no significant information as to prognosis. The prognosis became slightly less favorable if the pulmonary or the tricuspid valve was damaged. Auricular fibrillation developed in 42.8 per cent of the 644 cases. This arrhythmia was usually a late manifestation in rheumatic heart disease, and the highest incidence was found in cases of mitral stenosis. Auricular fibrillation per se did not determine prognosis or life expectancy.

It is important to distinguish, however, between children who have a first attack of rheumatic infection involving the heart and adults with chronic rheumatic valvular disease because of the fact that younger patients usually die of the rheumatic infection itself while older patients generally die of the late results in the form of heart failure.

SYPHILITIC DISEASE OF THE HEART AND AORTA

Maynard and his co-workers [35] have published a preliminary report of their investigation designed as a study of the natural history of syphilitic infection in relation to its effect on the cardiovascular system. Every syphilitic patient in the Brooklyn Hospital who consented was subjected to a complete cardiovascular examination. Of 346 patients thus examined, 145 (41.9 per cent) presented evidence of cardiovascular syphilis. This incidence is extremely high, but the criteria for diagnosis set by Maynard and his co-workers seem adequate. For example, all the patients with uncomplicated aortitis were known to have been syphilitic; none had suffered from rheumatic fever or arterial hypertension; none was over 49 years of age or presented any evidence of peripheral sclerosis, and all exhibited dilatation of the aorta.

---

34. Heart failure was considered to be present when symptoms of cardiac insufficiency were so pronounced that the patients were unable to do any work and had to go to bed and remain there for some time.

35. Maynard, E. P., Jr.; Curran, J. A.; Rosen, I. T.; Williamson, C. G., and Lingg, Claire: Cardiovascular Syphilis: Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis, Arch. Int. Med. **55**:873 (June) 1935.

Maynard and his co-workers divided their patients into five groups according to the interval between the appearance of a chancre and the time of the cardiovascular study. The incidence of cardiovascular syphilis among patients examined within the first three years was 14 per cent; among those examined within from four to nine years it was 28.6 per cent; among those examined within from ten to nineteen years, 56.8 per cent; among those examined within from twenty to twenty-nine years, 77.8 per cent, and among those examined within thirty or more years, 88.2 per cent. The incidence of symptoms increased progressively in the five groups; heart failure (congestive failure) was found to occur only in the patients in whom aortic insufficiency, aneurysm or involvement of a coronary artery developed. Maynard and his co-workers reached the important conclusion that "involvement of the aorta begins soon after the chancre has appeared and that, in the past, discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination." For final confirmation of this conclusion more pathologic study is required.

Padget and Moore [36] have analyzed the course of the disease in 161 patients with cardiovascular syphilis in respect to the effect of antisyphilitic treatment. About one third of the patients died in less than a year of observation; these were considered in a separate group, as unamenable to the beneficial effects of antisyphilitic therapy because of the gravity of their disease. Of the remaining two thirds, about half were considered as having had adequate, and half as having received inadequate, treatment. The "mean potential period" of observation was ten years and eight months. The number of deaths due to cardiovascular syphilis was found to be 1.62 times as great in the poorly treated as in the well treated patients with aneurysm, 2.46 times as great in those with aortic insufficiency and 2.06 times as great for the whole group. The duration of life from the onset of symptoms for the patients who died was found to be 1.47 times as great in the well treated as in the poorly treated patients for the whole group, 1.71 times as great in those with aneurysm and 1.37 times as great in the patients with aortic insufficiency. The importance of adequate treatment in cases of cardiovascular syphilis requires no comment.

Blackman [37] stated that while slight scarring along the edge of the mitral valve is not uncommonly found when syphilitic lesions of the

36. Padget, P., and Moore, J. E.: Results of Treatment in Cardiovascular Syphilis: Report of Three Years' Additional Observation, Am. Heart J. **10**: 1017, 1935.

37. Blackman, S. S., Jr.: Syphilis of the Mitral Valve and Membranous Interventricular Septum of the Heart, Bull. Johns Hopkins Hosp. **57**:111, 1935.

aortic valve are extensive, he has found only 1 report of a marked syphilitic lesion of the mitral valve. He described 2 additional cases in detail in which lesions of the mitral valve and membranous interventricular septum were directly continuous with syphilitic changes in the root of the aorta and aortic valves. Mitral lesions were suspected clinically in both cases in addition to aortic valvular disease.

Norris [38] found only 2 instances of syphilitic aortitis, presumably of congenital origin, in 14,000 autopsies performed at the Johns Hopkins Hospital. He pointed out that in order to prove without doubt that the condition in a certain case represents a congenital infection it is necessary to show that the patient's mother unquestionably had syphilis at the time of the child's birth and that the patient had other lesions of congenital syphilis or was known to have had a positive Wassermann reaction at an early age. However, in view of the great rarity of superinfection, it is reasonable to consider syphilitic aortitis with other manifestations of a congenital infection as being congenital. One of the author's cases occurred in a girl aged 9 years and the other in a youth aged 17. Both patients died suddenly, and necropsy revealed syphilitic aortitis and narrowing or occlusion of the coronary aorta.

Among 3,000 patients admitted to the wards of the medical service of the Baltimore City Hospitals there were 20, all under 46 years of age, suffering from marked cardiac decompensation unexplained by any of the usually accepted causes of heart disease.[39] All had positive Wassermann reactions. Five of the 20 died and were examined post mortem, and in none was any coronary sclerosis or valvular disease found. Microscopically, all showed extensive scarring and round cell infiltration of the myocardium. There was no sclerosis of the vessels of the kidneys, adrenal glands or other organs to suggest the possibility that a previous hypertension had existed. Magill suggested the possibility of syphilitic myocarditis.

MISCELLANEOUS INFECTIONS

Some years ago the important observations were made by Lewis and Grant that of an unselected series of patients with subacute bacterial endocarditis about one fourth present a congenitally bicuspid condition of the aortic valves and that about one fourth of those reaching adult life and having bicuspid aortic valves die of active endocarditis. Lewis and Grant necessarily concluded that the invasion of the blood stream by Streptococcus viridans is a common event, which in normal persons

38. Norris, Robert F.: Syphilitic Aortitis in Childhood and Youth: Report of Two Cases with Sudden Death, Bull. Johns Hopkins Hosp. **57**:206, 1935.

39. Magill, T. P.: Syphilitic Myocarditis, Bull. Johns Hopkins Hosp. **57**: 22, 1935.

is without evil results. Okell and Elliott[40] sought to determine, by direct observation, the frequency with which Str. viridans enters the blood stream of the average person. They expressed the belief that this organism is found chiefly in the mouth and most frequently in cases of infection of the gums and that it is found elsewhere only in small numbers and under exceptional conditions. They found a streptococcic bacteremia in 10.9 per cent of a group of persons with infected mouths. Shortly after the extraction of teeth from obviously infected mouths a transient streptococcic bacteremia lasting a few minutes occurred in three fourths of their patients. In persons without obvious disease of the gums, extraction of teeth was followed by a transient bacteremia in about one third of the patients. These observations were based on the examination of the blood on a single occasion, and the organisms isolated from the blood were usually streptococci (Str. viridans) which were culturally and serologically similar to strains obtained from the mouth. This observation points to the importance of early prophylactic care of the teeth and gums, particularly in children with rheumatic or congenital heart disease.

Von Glahn and Pappenheimer,[41] from pathologic observations on a series of 26 consecutive cases of subacute bacterial endocarditis, reached the opinion "that active rheumatic vegetations are, in persons who have had rheumatism, a necessary and practically constant prerequisite for the implantation of the bacteria." They summarized the evidence for this conclusion as follows:

1. Vegetations histologically identical with those in rheumatic endocarditis and not containing bacteria are found (*a*) on the same valve as the bacterial vegetations, (*b*) on other valves on which there are no vegetations containing bacteria and (*c*) on the auricular wall.

2. Aschoff bodies in the myocardium that are taken to indicate active rheumatic disease are found in practically the same proportion of cases of subacute bacterial endocarditis as of uncomplicated rheumatic cardiac disease.

3. Types of bacterial endocarditis other than that due to nonhemolytic streptococci may be engrafted on active rheumatic vegetations. This is a cogent argument against the view that the two types of lesions are a response of different intensity to the same infective agent, unless we dispense with current views as to the histologic specificity of the rheumatic reaction.

They rightly emphasized that bacterial infection of the valves is not always the result of implantation on unhealed rheumatic lesions. Furthermore, there may be added the possibility that a recrudescence of rheumatic fever may occur after subacute bacterial infection which

40. Okell, C. C., and Elliott, S. D.: Bacteriaemia and Oral Sepsis with Special Reference to the Aetiology of Subacute Endocarditis, Lancet **2**:869, 1935.

41. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **55**:173 (Feb.) 1935.

was superimposed on a healed rheumatic lesion. This would equally well explain the association of active rheumatic carditis and subacute bacterial endocarditis.

Baker [42] has reviewed the subject of endocardial tuberculosis and added his own observations. Tuberculous endocarditis was found 6 times in about 900 consecutive necropsies at Duke Hospital. In 5 instances there were small scattered tubercles occurring on all parts of the endocardium as part of a generalized miliary infection. In one instance the endocardial process resulted from the extension of pericardial and myocardial tuberculosis through the cardiac wall. Baker expressed the belief that the tubercles probably arise by implantation via the blood stream, but endocardial lesions may also develop by extension from the myocardium. A critical survey of reported cases of tuberculous endocarditis as a diffuse process at the line of closure of the valves reveals only 1 case in which the diagnosis is probably correct. The toxic action of a tuberculous process somewhere in the body does not result in sclerosis of the endocardium or healed fibrous or calcified valvular lesions.

In the past three years Spink [43] has observed 35 sporadic cases of trichinosis. Although clinical evidence of myocardial damage was present in only 1 case, abnormal electrocardiographic changes were noted in 6 of the 18 cases in which this test was performed. The electrocardiographic abnormalities included changes in the T wave and low amplitude and abnormal duration of the QRS complex. Spink expressed the belief that the acute myocarditis occurring in cases of trichinosis may be a nonspecific inflammatory reaction due to the invasion of the myocardium by larvae.

THE HEART IN THYROID DISEASE

Nahum and Hoff [21] injected 50 mg. of acetyl-β-methylcholine chloride into a patient with hyperthyroidism suffering from auricular flutter with 2:1 block. Gradually the block increased to 4:1 and then to 5:1, and soon auricular fibrillation supervened. An hour and a half later, when the effect of the injection could be expected to have worn off, a normal slow supraventricular rhythm spontaneously reappeared.

Stimulated by this interesting observation, Nahum and Hoff sought to discover whether acetyl-β-methylcholine chloride might play a similar rôle in converting the normal heart mechanism in patients with hyperthyroidism into auricular fibrillation. Accordingly 5 patients with normal cardiac rhythm were given 0.75 mg. of the drug per kilogram of body weight, and continuous electrocardiograms were made. In 4

42. Baker, R. D.: Endocardial Tuberculosis, Arch. Path. **19**:611 (May) 1935.

43. Spink, Wesley W.: Cardiovascular Complications of Trichinosis, Arch. Int. Med. **56**:238 (Aug.) 1935.

patients definitely suffering from hyperthyroidism short periods of auricular fibrillation appeared, but this was not observed in 1 patient with doubtful hyperthyroidism. The normal cardiac mechanism reappeared from five to twenty minutes later. Since the acetylcholine derivative reproduces the same effects on the pacemaker and auricle of the heart as stimulation of the vagus nerves, Nahum and Hoff concluded that one factor in the spontaneous production of auricular fibrillation is the action of the vagus nerves on the heart. However, the failure to produce auricular fibrillation in normal persons with the same or even with larger doses of the drug makes it seem obvious that thyroxine is an additional factor which acts with the vagus nerve. The widespread occurrence of auricular fibrillation in persons not suffering from hyperthyroidism indicates that agents other than thyroxine may operate with the vagus factor to induce and maintain this disorder. The authors found that in cats electric shock may produce auricular fibrillation when acting with the vagus factor. It is suggested that in cases of mitral stenosis stretching or inflammation of the auricle, in cases of hypertension vagal overactivity and in cases of congestive failure distention of the auricle may be a significant factor.

On the basis of their own studies and of those reported by other investigators, Boothby and Rynearson [44] showed that the increase in the circulatory rate in patients with exophthalmic goiter who are not treated with iodine is much greater than that which occurs in normal persons as the result of an increase in oxygen consumption due to work. The same is true in lesser degree for patients receiving iodine treatment. These facts suggest to the authors the hypothesis that in persons with exophthalmic goiter there is a peculiar circulatory stimulant which causes a greater increase of the circulatory rate than occurs in a normal subject as a result of a corresponding increase in oxygen consumption. After effective iodine medication this stimulant is decreased in amount, or its effectiveness is lessened.

There have been a number of interesting clinical reports [45] concerning various phases of the relationship between the heart and thyroid disease; a few are mentioned by title.

---

44. Boothby, Walter M., and Rynearson, Edward H.: Increase in Circulation Rate Produced by Exophthalmic Goiter Compared with That Produced in Normal Subjects by Work, Arch. Int. Med. **55**:547 (April) 1935.

45. Viethen, A.: Herzverengung bei Morbus Basedow in Kindern, Monatsbl. f. Kinderh. **64**:81, 1935. Margolies, A.; Rose, E., and Wood, F. C.: The Heart in Thyroid Disease: I. The Effect of Thyroidectomy on the Orthodiagram, J. Clin. Investigation **14**:483, 1935. Rose, E.; Wood, F. C., and Margolies, A.: The Heart in Thyroid Disease: II. The Effect of Thyroidectomy on the Electrocardiogram, ibid. **14**:497, 1935. Sise, L. F.: Anesthesia for Thyrocardiac Patients, J. A. M. A. **105**:1662 (Nov. 23) 1935. Parade, G. W.: Relative Aorteninsuffizienz bei Morbus Basedow, Deutsche med. Wchnschr. **61**:1799, 1935. Wiechmann, E.: Relative Aorteninsuffizienz bei Basedow, ibid. **61**:10, 1935.

PERICARDIAL DISEASE

Chronic constrictive pericarditis, commonly called Pick's disease, may be cured by surgical means. This fact has stimulated much interest in the disease,[46] and the comprehensive clinical report by White [47] may be profitably reviewed.

He defined chronic constrictive pericarditis as a

> chronic fibrous or callous thickening of the wall of the pericardial sac which is so contracted that the normal diastolic filling of the heart is prevented. A condition called "inflow stasis" results. There may or may not be calcification of the pericardium, obliteration of the pericardial cavity, or important external pericardial adhesions. There may or may not be an associated accumulation of pericardial fluid in small amounts, as in pockets. The parietal pericardium may be preponderantly affected or the epicardium also seriously involved; or both pericardial membranes may be securely or even inseparably united. One section of the pericardium, as over the cardiac apex, may remain relatively free and but slightly thickened, while the other part, as over the right auricle and great veins, is markedly contracted; or the entire heart and roots of the great vessels may be encased uniformly in a tightly fitting envelope. There may or may not be an acute or chronic polyserositis, which is, contrary to a common belief, a different thing. There may or may not be frosted liver or spleen. There may or may not be heart disease itself—. . . the association of chronic constrictive pericarditis, of any important degree at least, with heart disease is very rare.

From a study of 15 cases, which are reported in detail, it is emphasized that in diagnosis

> . . . one should take into consideration not only individual signs alone but the entire clinical picture and history of the case. The leading clues are the result of "inflow stasis," namely (1) the insidious onset of dropsy in a young person, (2) preponderant liver enlargement and ascites, (3) increased prominence of the jugular veins, (4) normal or relatively normal heart in the presence of dropsy without nephritis, and (5) low blood and pulse pressure and paradoxical pulse. Other important clues are (6) X-ray evidence (poor pulsation, calcification, chronic pleuritis), (7) electrocardiographic abnormalities (low voltage or "coronary" T waves in chronic disease in early youth), and (8) a previous history of acute pericarditis or polyserositis.
>
> Chronic constrictive pericarditis has been confused with four other conditions, but with ordinary care and thought such errors of diagnosis should not arise. The four conditions are mitral stenosis, polyserositis (including instances of perihepatitis or frosted or iced liver—Zuckergussleber), primary cirrhosis of the liver, and nutritional oedema. Two other conditions—namely, tricuspid stenosis and mediastinal tumors—may also cause some of the same signs.
>
> The prognosis of cases with chronic constrictive pericarditis for good health is poor unless suitable for, and submitted to operation, although mild or only

46. Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, Arch. Int. Med. **56**:250 (Aug.) 1935. Winkelbauer, A., and Schur, M.: Surgical Therapy of Adherent Pericarditis, Med. Klin. **31**:1269, 1935. Beck, C. S.: Two Cardiac Compression Triads, J. A. M. A. **104**:714 (March 2) 1935.

47. White, P. D.: Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection, Lancet **2**:539 (Sept. 7); 597 (Sept. 14) 1935.

moderately severe cases may live for many years a semi-invalid requiring much rest and frequent or occasional abdominal paracenteses.

Cure is now possible by surgery and an imposing number of successful cases of pericardial resection (by the Delorme operation, and not by that proposed by Brauer) is being accumulated. In our own clinic twelve cases have had this operation performed, ten by one surgeon; of these latter ten cases, six have been completely cured and one other relieved to a high degree. The first successful case in America, operated on seven years ago in 1928, belongs to this group; this patient, a young woman, is in excellent health to-day, as are the other five cases of complete cure.

Nothing of especial importance or interest has been published on acute pericarditis.

CARDIAC TRAUMA

Bright and Beck [48] have made an interesting and important study of wounds of the heart produced by contusive or compressive forces. They expressed the belief that the thoracic cage by no means perfectly protects the heart and that this organ is the recipient of many injuries, which are rarely recognized. The heart, lying against the sternum, is vulnerable to any sudden impact over the sternum and, buttressed against the bodies of the thoracic vertebrae posteriorly, is vulnerable to compression forces applied to the chest.

They have comprehensively reviewed and analyzed the medical literature pertaining to nonpenetrating cardiac wounds and classified the various ways in which such wounds may be produced.

I. A direct blow over the precordium producing fracture of sternum or ribs, the broken ends of which are driven into the heart . . .

II. Contusion or compression of the heart between the sternum anteriorly and the vertebrae posteriorly . . .

III. The application of indirect forces, such as by the sudden compression of the legs and abdomen . . .

IV. Laceration of the thoracic viscera, such as may be sustained in a fall from a high building . . .

V. Concussion of the heart . . .

In the analysis of 175 cases they found that when the heart receives a contusion the result may be: (1) rupture of the heart (152 instances); (2) myocardial failure without rupture (11 instances), or (3) recovery (12 instances). It is pointed out that these proportions do not represent the correct relative incidence of these three types of sequelae to contusion because many patients recover without the correct diagnosis having been made. In a consideration of the 152 cases of rupture of the heart, it was found that the four cardiac chambers seem to be equally vulnerable. The right auricle was ruptured in 36 cases, the left

48. Bright, E. F., and Beck, C. S.: Nonpenetrating Wounds of the Heart: A Clinical and Experimental Study, Am. Heart J. **10**:293, 1935.

auricle in 30, the right ventricle in 31 and the left ventricle in 37. More than one chamber was ruptured in 13 cases. The chief clinical manifestations were those of sudden collapse. Some patients complained of precordial pain, or the pain was referred to the heart, to the left side or to the shoulder. The pulse was either slow or rapid, but as the pressure in the pericardial cavity increased, the pulse became feeble. Vomiting and headache sometimes occurred. In some patients restlessness, anxiety and air hunger developed. The cardiac sounds became distant and even inaudible. As the blood pressure fell, the skin became cold and blanched, and finally unconsciousness supervened.

In the majority of patients in this group death was due to hemocardiac tamponade. In the group of 152 patients death occurred immediately after the accident in 47; 42 survived for a period the length of which was not mentioned, but the interval was undoubtedly short. Only a few patients survived more than two weeks, and these died within two months.

In regard to treatment, the authors expressed the opinion that in the group of 152 cases there were 30 in which it seemed that operation offered some chance of success. The operative treatment is discussed.

In order to study better the effect of contusions on the heart, Bright and Beck performed a series of 25 experiments on dogs by exposing the heart and applying contusive injuries to the myocardium. When the right or left ventricle was struck a number of blows, the heart rate became rapid, the myocardium became swollen from hemorrhage, usually there was some dilatation and not infrequently a hemorrhagic effusion developed. The electrocardiogram showed changes similar to those observed in disease of the coronary arteries. Although it appeared as if softening and rupture would surely follow, death occurred in only 5 instances. The cause of death was rupture in 1 instance, ventricular fibrillation in 2 and myocardial failure in 2.

On the basis of their experimental study the authors concluded that the heart can tolerate a great amount of trauma and that rupture is a rare complication. They expressed the belief that the vast majority of nonpenetrating wounds of the heart are not recognized clinically. The patients recover, and as the correct clinical diagnosis is not usually made their cases do not find the way into medical reports.

PULMONARY DISEASE AND THE HEART

Brenner [49] has written a comprehensive treatise on the pathology of the vessels of the pulmonary circulation based on a study of the

49. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation: I, II, III, IV and V, Arch. Int. Med. **56**:211 (Aug.); 457 (Sept.); 724 (Oct.); 976 (Nov.); 1189 (Dec.) 1935.

results of 100 consecutive unselected autopsies; the paper is one which any person especially interested in this field may profitably read.

The immediate effect of a high degree of occlusion of the pulmonary artery on the heart results in a condition which McGinn and White[50] have termed "acute cor pulmonale." Nine cases of the condition, in which it resulted from pulmonary embolism, are reviewed in detail and summarized as follows:

2. . . . The symptoms and signs of extensive pulmonary embolism are variable, but predominating at first are those of shock—namely, collapse, pallor, sweating, apprehension, and a fall in blood pressure—to be followed by reaction to the infarction itself—namely, fever and elevation of the pulse and respiratory rates. In none of our cases did we find acute chest pain in the absence of pleural involvement, but most of the patients complained of substernal oppression and suffocation. Respiratory distress was marked in all cases.

3. If the state of shock from extensive pulmonary embolism is not too great, or after it has largely cleared, there may be found signs indicative of the secondary effect of the pulmonary embolism on the heart itself: that is, the acute cor pulmonale (dilatation of the right chambers) attended by pulmonary artery dilatation. Auscultation in our cases frequently showed accentuation of the pulmonary second sound, gallop rhythm heard best in and just below the pulmonary valve region, and in two cases a "pericardial" friction rub with maximal intensity in the region of the second, third and fourth interspaces. Cyanosis and engorgement of the neck veins were common manifestations at some time during the attack. These changes remained for only a short period in some cases. Pleural friction rubs were heard frequently.

4. Electrocardiograms taken soon after the occurrence of the pulmonary embolism showed similar changes in five of our patients, and in two others taken some time after the attack they had some of the characteristics, although they were less definite. The changes that appear significant are the presence of a Q wave and late inversion of the T wave in lead 3, the rather low origin of the T wave with a gradual staircase ascent of the ST interval in lead 2, a prominent S wave and a slightly low origin of the T wave in lead 1, and an upright T wave (with inverted P and QRS waves) in lead 4. In none of our cases was left axis deviation present at any time of the acute episode, whereas the tracings of two patients showed definite right axis deviation.

Electrocardiograms of two patients taken after recovery showed a complete disappearance of the changes already mentioned, and in a third patient there was almost a complete disappearance of abnormalities in a record taken forty-eight hours after the attack and twenty-seven hours after the first electrocardiogram. All three of these cases showed a change in the axis deviation; one had a prolonged PR interval, and in one case in lead 4 the T wave was reverting to normal (inverted). Our follow-up studies indicate that the electrocardiographic changes are temporary and may disappear within forty-eight hours after the attack of pulmonary embolism.

5. It is probable that the changes observed clinically and the electrocardiographic variations in cases showing the acute cor pulmonale consequent on pul-

50. McGinn, Sylvester, and White, Paul D.: Acute Cor Pulmonale Resulting from Pulmonary Embolism: Its Clinical Recognition, J. A. M. A. **104**:1473 (April 27) 1935.

monary embolism are due in large part to dilatation and partial failure of the chambers of the right side of the heart.

Air embolism [51] is an uncommon but extremely interesting disorder. Different mechanisms have been suggested as being responsible for death, namely, cerebral or coronary air embolism of suffocation from obstruction of the pulmonary artery. If air is injected into a systemic vein, it collects in the pulmonary artery and its branches and does not accumulate in the heart or elsewhere until the volume injected exceeds the volume of the pulmonary artery and its branches. Consequently large amounts are well tolerated before suffocation occurs. However, as little as 1 cc. of air introduced into one of the pulmonary veins may cause fatal coronary or cerebral embolism. It is only natural, therefore, that surgeons who operate on the chest and those employing pneumothorax therapy encounter this complication more frequently than others. The clinical picture of coronary air embolism is variable, but it is usually that of severe shock. The electrocardiogram may show changes similar to those seen in cases of coronary infarction.

SYNCOPE

Weiss [52] has written an excellent authoritative account of syncope and related syndromes. The various types of syncope are separated according to the underlying physiologic mechanism so far as that is possible. Incidence, pathogenesis, clinical manifestations and treatment of the several types are considered.

Ferris, Capps and Weiss [53] have sought to clarify the mechanism involved in the so-called "cerebral type" of syncope due to involvement of the carotid sinus. This form of syncope occurs spontaneously and can be reproduced in susceptible persons; it results not from bradycardia or a fall in blood pressure but apparently from some reflex action on the central nervous system. Extensive studies on 32 patients permitted the authors to reach important conclusions. Of particular interest in this connection is the fact that digitalis has been found to have a sensitizing effect not only on the usual carotid sinus reflex but also on the carotid sinus cerebral reflex. The authors expressed the belief that this possi-

51. Wolffe, J. B., and Robertson, H. F.: Experimental Air Embolism, Ann. Int. Med. **9**:162, 1935. Durant, T. M.: The Occurrence of Coronary Air Embolism in Artificial Pneumothorax, ibid. **8**:1625, 1935.

52. Weiss, S.: Syncope and Related Syndromes, in Christian, Henry A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1929, vol. 3, pt. 1., p. 250.

53. Ferris, E. B.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, Medicine **14**:377, 1935.

bility must be kept in mind when digitalizing elderly patients, as it may cause not only powerful cardiac inhibition but also vasomotor depression.

ARTERIAL HYPERTENSION

The interdependence between renal function in its widest meaning and arterial hypertension is being studied by several groups of investigators in different countries. The published results are extremely discordant but are of great interest because of the importance of the problem. Many workers, especially in America and in England, have been busy merely disproving the claims and theories of other investigators.

It has been shown that arterial hypertension can be experimentally produced by various procedures which injure the kidney, such as destroying or removing a considerable portion of the renal tissue or reducing the blood flow by compression of the renal artery. It has been suggested that the hypertension so produced may be due to failure in the excretion of certain pressor substances in the blood, to interference with the elaboration of certain pressor or depressor "hormones" or to reflex action on the vasomotor center.

It has been claimed, furthermore, that experimental hypertension brought on by the injection of kaolin into the cisterna magna or by denervating the carotid sinus and cutting the depressor nerves is dependent on the intact nerve supply to the kidneys. Thus in dogs in which the blood pressure is raised as a result of injection of kaolin the pressure is said to fall if one kidney is denervated but to rise again if the denervated kidney is removed.

Braun and Samet [54] presented protocols of experiments on dogs whereby increased arterial blood pressure was produced either by injection of kaolin or by cutting depressor nerves. The hypertension was quickly abolished after denervation of one or both kidneys, whereas the denervation of other vascular areas was without effect. Also, preliminary denervation of the kidneys prevented any rise in blood pressure.

Pick [55] produced experimental hypertension in dogs by injecting kaolin into the cisterna magna and then found that 20 cc. of blood from one of these animals injected into a normal dog raised its blood pressure for several days. However, this rise of blood pressure in the second dog could be abolished by injecting 20 cc. of blood from a dog after the kidneys had been denervated. Pick expressed his intention

54. Braun, L., and Samet, B.: Experimentelle Untersuchungen über die Beziehungen zwischen Blutdruck und Niere, Arch. f. exper. Path. u. Pharmakol. **177**: 662, 1935.

55. Pick, E. P.: Ueber humorale Uebertragung hohen und niedrigen Blutdrucks, Wien. klin. Wchnschr. **48**:635, 1935.

to investigate further the mechanism involved, including the possibility of depressor hormones being elaborated by a denervated kidney.

Page [56] has investigated the suggestion that elevation of blood pressure associated with either inflammatory or vascular disease of the kidneys may be due to nervous impulses originating in the kidneys and conducted by way of the extrinsic renal nerves to the vasomotor centers. He found that the hypertension produced in dogs by constricting the renal arteries or by irradiating the kidneys was not affected by preliminary stripping of the renal pedicle of its extrinsic nerve supply. He concluded that these nerves do not appear to participate in the genesis of renal hypertension, at least of these types. Hypertension produced by constriction of the renal arteries did not cause significant changes in renal efficiency.

Acting on the supposition that the unknown cause of essential hypertension may lie in nervous impulses from the kidney, Page and Heuer [57] performed bilateral denervation of the kidney on a patient with essential hypertension uncomplicated by detectable renal involvement. No change in the level of arterial blood pressure resulted, and consequently there was no support for the hypothesis underlying the procedure. No ill effects, either renal or extrarenal, were observed after the denervation.

The hypothesis of Volhard that hypertension of renal origin is caused by pressor substances circulating in the blood has received apparent experimental support from workers in his laboratory and elsewhere. The evidence on which this hypothesis rests has naturally been subjected to critical repetition by many investigators, and during the past year careful studies have been reported,[58] which have in common the conclusion that there is no increase in pressor substances in the blood of patients with hypertension of any type.

This whole problem of essential hypertension and hypertension in relation to renal disease is still unsettled. New theories are advanced faster than old ones can be disproved. The recent experimental studies are extremely interesting, and it is of the greatest significance that

56. Page, Irvine H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, Am. J. Physiol. **112**:166, 1935.

57. Page, Irvine H., and Heuer, George J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, J. Clin. Investigation **14**:27, 1935.

58. Aitken, R. S., and Wilson, C.: An Attempt to Demonstrate a Pressor Substance in the Blood in Malignant Hypertension, Quart. J. Med. **4**:179, 1935. Capps, R. B.; Ferris, E. B., Jr.; Taylor, F. H. L., and Weiss, Soma: Rôle of Pressor Substances in Arterial Hypertension, Arch. Int. Med. **56**:864 (Nov.) 1935. Page, Irvine H.: Pressor Substances from the Body Fluids of Man in Health and Disease, J. Exper. Med. **61**:67, 1935.

permanent arterial hypertension, obviously of renal origin, can be produced in dogs without there being significant evidence of renal insufficiency.

CORONARY ARTERIOSCLEROSIS

For nearly thirty years it has been known that the feeding of cholesterol or of foods rich in cholesterol results in the development of widespread lesions of the arteries in rabbits. The similarity between these lesions and the lesions typical of human arteriosclerosis stimulated immensely the study of experimental arteriosclerosis caused by cholesterol, and the results of this study have been applied directly to man by many investigators. Duff [59] has critically examined the entire problem with the purpose of determining what facts have been established and of evaluating their importance as applied to the solution of problems of arteriosclerosis in man. It is distinctly worth while to review his paper in some detail.

When rabbits have been given cholesterol for some time, lesions of the arteries appear. The first lesions appear in the arch of the aorta about the mouths of the vessels arising from it or just above the aortic valve ring. Lesions appear later in other portions of the aorta and its larger branches, and finally the smaller branches may show nodular lesions. The coronary arteries are often attacked. The nature of the lesions seems to be essentially the same wherever they occur. The first visible alteration is a swelling of the ground substance, which is normally a thin layer separating the lining endothelium from the internal elastic lamina. Here the deposition of lipoids may become abundant, and it seems probable that they consist chiefly of cholesterol and its esters. These deposits stir into activity numerous macrophages, which are attracted to the site and which then engulf a large part of the lipoid material. With the development of the lesions, necrotic areas appear, and there is extensive fibroblastic proliferation. Medial lesions occur and may be independent of intimal lesions, although they are commonly associated with them. After the administration of cholesterol is discontinued, the arterial lesions are found to persist to the end of the longest experiments, but they show evidence of transition toward a more fibrous type.

The method of cholesterol feeding has been applied to a variety of experimental animals other than rabbits. Although arterial lesions have been produced with difficulty in guinea-pigs, there has been no convincing demonstration of a similar effect in any other animal. Intensive and prolonged feeding of cholesterol does not affect in any way the arteries of cats, dogs, foxes or monkeys. It is interesting to consider

59. Duff, G. Lyman: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. **20**:81 (July); 259 (Aug.) 1935.

further various factors influencing the development of cholesterol-induced arteriosclerosis in the rabbit.

Whereas the continued feeding of cholesterol is incapable of producing any striking sustained rise in the cholesterol content of the blood in animals such as dogs, in rabbits, on the contrary, the cholesterol content of the blood is raised to many times the normal value. This is probably because the mechanism for handling exogenous cholesterol is amply sufficient in animals such as dogs, whereas it is deficient in rabbits.

Certain facts, however, have suggested that some factor in addition to cholesterol feeding with resulting hypercholesteremia is necessary or important to the development of the arterial lesions. Hypercholesteremia, for example, may develop in the rabbit without producing any changes in the arteries within the usual experimental period. Furthermore, the patchy distribution of the lesions when they are produced suggests some preceding local condition in the involved areas which favors the precipitation of lipoids.

The question of the possible influence of rises in blood pressure has been considered, but there is no satisfactory evidence to show that an increase in blood pressure can affect the progress of the arterial lesions.

Of especial interest is the fact that extirpation of the thyroid gland has been found to facilitate the development of the lesions without significantly affecting the curve for cholesterol content of the blood. The feeding of thyroid extract in conjunction with cholesterol retards the progress of the lesions, but in animals receiving that mixed regimen the resulting hypercholesteremia is much less extreme than that which occurs in control animals fed cholesterol alone. It has been further shown that large doses of organic iodine compounds or of potassium iodide retard or even prevent the development of experimental cholesterol-induced arteriosclerosis in rabbits, owing apparently to the fact that the administration of the iodine greatly diminishes the hypercholesteremia, although this explanation is not accepted by all observers.[60] The possibility that the iodine compounds act through an influence on thyroid activity has been shown to be the case, for the prophylactic effect is abolished by thyroidectomy. It has been shown recently [61] that iodine has no influence on the involution of vascular lesions previously produced by the feeding of cholesterol.

60. Page, I. H., and Bernhard, W. G.: Cholesterol-Induced Atherosclerosis: Its Prevention in Rabbits by the Feeding of an Organic Iodine Compound, Arch. Path. **19**:530 (April) 1935.

61. Meeker, D. R.; Kesten, H. D., and Jobling, J. W.: Effect of Iodine on Cholesterol-Induced Atherosclerosis, Arch. Path. **20**:337 (Sept.) 1935.

Various noxious agents which have in common the ability to injure the arterial walls have been shown to facilitate the development of arterial lesions; among those tested have been mechanical injury, nicotine, epinephrine, viosterol and bacteria.

It may be safely concluded that in rabbits hypercholesteremia is a necessary prerequisite for the formation of lipoid deposits in the arterial walls, but in addition some unknown factor inherent in the experimental procedure produces an injury to the walls of the arteries. This injury is responsible for the local histologic changes which precede the appearance of lipoid deposits and is essential for their deposition.

Of chief concern are the significance of the aforementioned experimental data in regard to the etiology of human arteriosclerosis. Certain important differences between man and the rabbit in this connection may be pointed out.

Although the anatomic lesions, especially the intimal lesions, of experimental arteriosclerosis are similar to those of the disease in man, important differences are noted, especially in regard to the distribution of lesions, and the medial sclerosis which may be a feature in the early stages of the disease in rabbits. These and other differences between the two types of lesions require caution against the hasty conclusion that their etiology is identical or that etiologic factors which may be common to them must operate with equal intensity in the two instances.

Three main factors seem implicated in the production of the lesions in rabbits, namely, the cholesterol-rich diet, hypercholesteremia and the occurrence of injury to the arteries. Certain differences between the rabbit and man indicate that these factors do not operate in man in exactly the same way as in the rabbit.

The rabbit is a herbivorous animal, and vegetable diets are cholesterol-poor; man, on the contrary, is omnivorous, and varying quantities of cholesterol are contained in his normal diet. The rabbit excretes exogenous cholesterol with difficulty, and hypercholesteremia can be easily produced; in the case of man, however, large quantities of cholesterol in the diet have only a relatively slight and temporary effect on the level of cholesterol in the blood, owing to the ease with which cholesterol is excreted. The normal cholesterol content of human blood is approximately twice as great as that of rabbit's blood, and spontaneous arterial lesions are characterized in man by accumulations of lipoids, while in the rabbit no such accumulations occur. Elevation of the normal cholesterol level of the blood is necessary to the development of the fatty arterial lesions in rabbits, whereas in man hypercholesteremia is not found with any regularity in association with arteriosclerosis.

The occurrence of preliminary local alterations in the walls of human arteries before the formation of lipoid deposits may be regarded as an established fact, and this is likewise an essential factor in the develop-

ment of the experimental lesion in the rabbit. Thus, with respect to the primary local changes in the arterial walls, experimental cholesterol-induced arteriosclerosis in the rabbit may well be compared with arteriosclerosis in man. Many of the experimental measures which have been employed for the production of injury to the arteries of rabbits seem to have no direct significance as applied to man, owing to the fact that the arteries of rabbits are extraordinarily susceptible to injury, but this does not detract from the general conclusion that the local alterations leading to lipoid deposition are the result of some sort of injury.

Duff concluded that experiments on cholesterol feeding provide no valid reason for believing that a disturbance of cholesterol metabolism plays any part in the etiology of human arteriosclerosis. The cause of the arterial injury which initiates the development of human arteriosclerosis is obscure, and the experiments on cholesterol feeding provide hardly any suggestive information bearing on this most important problem.

We are inclined to agree with Duff, but needless to state there is a competent body of medical opinion which does not subscribe to his main conclusions. During the past year Leary [62] has again presented his arguments that atherosclerosis is a metabolic disease.

There have been a number of interesting clinical and experimental studies [63] relating to the coronary circulation, cardiac pain and myocardial infarction which, owing to considerations of space, cannot be reviewed.

---

62. Leary, Timothy: Pathology of Coronary Sclerosis, Am. Heart J. **10**:328, 1935; Atherosclerosis: The Important Form of Arteriosclerosis; a Metabolic Disease, J. A. M. A. **105**:475 (Aug. 17) 1935.

63. Green, Charles W.: The Nerve Control of the Coronary Vessels with New Experimental Evidence for the Pathways of Efferent Constrictor and Dilator Neurones in the Dog, Am. J. Physiol. **113**:361, 1935; Control of the Coronary Blood Flow by Reflexes Arising in Widely Distributed Regions of the Body, ibid. **113**:399, 1935. Katz, L. N.: Mechanism of Pain Production in Angina Pectoris, Am. Heart J. **10**:322, 1935. Katz, Louis N.; Mayne, Walter, and Weinstein, William: Cardiac Pain: Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, Arch. Int. Med. **55**:760 (May) 1935. Kisch, F.: Angina Pectoris im Arbeitstest, Klin. Wchnschr. **14**:1165, 1935. Leriche, R., and Fontaine: Contribution expérimentale à l'étude de la circulation coronarienne chez l'animal entier: Le rôle du sympathique dans l'innervation des coronaires, Ann. de méd. **37**:407, 1935. Nemet, G., and Gross, H.: Interrelationship of Arteriosclerotic Heart Disease and Chronic Congestive Failure, Am. Heart J. **10**:643, 1935. Nuzum, F. R.; Elliott, A. H., and Evans, R. D.: A Clinical and Pathological Study of Coronary Sclerosis: Its Incidence in Hypertension and Angina Pectoris, ibid. **10**:367, 1935. Robertson, Harold F.: The Reestablishment of Cardiac Circulation During Progressive Coronary Occlusion, ibid. **10**:533, 1935. Shambaugh, Philip: Circulatory Changes in Angina Pectoris: An Experimental Study, Arch. Int. Med. **56**:59 (July) 1935. Tennant, R., and Wiggers, C. J.: The Effect of Coronary Occlusion on Myocardial Contraction, Am. J. Physiol. **112**:351, 1935.

Of especial interest are the findings of Saphir and his co-workers[64] based on a study of 34 cases selected by a pathologist without previous knowledge of the clinical and electrocardiographic findings. After the anatomic material had been studied, the clinical and electrocardiographic records were reviewed, and the attempt was made to correlate the findings thus obtained with the anatomic lesions.

Both coronary arteries were found to be involved, and some degree of myocardial fibrosis was present in all hearts examined. The most severe lesions were found in the left coronary artery, especially in the descending branch. Myocardial infarcts were noted in 28 instances, and at least two branches of the coronary arteries supplying the infarcted areas were involved. In 4 hearts, infarcts were present without any occlusion of the coronary arteries, although their lumens were markedly narrowed. Such infarcts were probably caused by transient myocardial insufficiency, which in the presence of narrowed coronary arteries led to a temporarily inadequate blood flow.

Saphir and his co-workers found that the electrocardiogram may fail to give any clue to the full significance of previous clinical attacks and does not always aid in determining whether or not coronary thrombosis or myocardial infarction is present. Furthermore, it was not found possible to locate the position of the infarct from electrocardiographic records obtained with the standard three leads.

Pain referable to the heart occurred in only 18 of their 34 patients, but coronary thrombosis was encountered 32 times; there were only 4 instances in which an attack of pain unrelated to effort could reasonably be correlated with the occurrence of coronary thrombosis or myocardial infarction. On the other hand, coronary sclerosis and myocardial fibrosis alone were present in 4 instances at the time attacks of pain unrelated to obvious effort occurred. Saphir and his co-workers found the duration and severity of pain to be unreliable guides in diagnosing coronary thrombosis.

Not coronary thrombosis nor myocardial infarction nor coronary arteriosclerotic occlusion can be the anatomical equivalent of angina pectoris because these lesions were found not only in the presence of angina pectoris but also in patients who never had attacks of angina pectoris. Besides, these lesions were not constantly present in hearts of patients dying following attacks of angina pectoris. Only one anatomical change was common to all hearts of patients who had attacks of angina pectoris, namely, coronary sclerosis and myocardial fibrosis. To the morphologist, coronary sclerosis and fibrosis of the heart mean a labile myocardium which may fail suddenly. It seems that the sudden failure, or the subsequent events, is intricately linked with anginal attack in some manner as yet undetermined.

64. Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, Am. Heart J. **10**:567 (June); 762 (Aug.) 1935.

In the present state of our knowledge, it appears impossible to differentiate clinically between myocardial infarction brought about by coronary thrombosis and that following arteriosclerotic narrowing or occlusion of the coronary arteries. It is also difficult to determine the occurrence of coronary thrombosis and myocardial infarction clinically, either because the thrombosis and infarct may occur "silently," or because the characteristic picture may be found in the absence of thrombosis and infarction.

Beck and his associates [65] have concerned themselves for some time with the problem of increasing the blood supply to the heart by operation. Their first studies were made on dogs in which the epicardium and the lining of the parietal pericardium of the heart were removed and adhesions were allowed to form between the myocardium and the vascular bed afforded by the parietal pericardium and pericardial fat. A pressure differential was found necessary to promote anastomosis between the cardiac and the extracardiac vascular bed, which was provided by reducing the normal coronary blood supply. After the establishment of the collateral circulation it was found possible to reduce greatly the lumen of the right or left coronary artery near the aorta without fatally injuring the heart.

Further experiments were carried out, in which pedicle grafts of muscle together with the pericardial and mediastinal fat were used for the vascular bed. Anastomoses readily developed between skeletal and cardiac muscle if a sufficient pressure differential was provided. When the collateral vascular supply was well established it was possible to ligate the right coronary artery or the descending branch of the left coronary artery without producing a fatal injury, provided the ligation was carried out in two stages. From a clinicopathologic study of human material it was judged that nearly half of the patients would have been suitable subjects for operation and might have benefited by the production of the extracardiac collateral circulation. Pedicle grafts of pectoral muscle were sutured to the circumflex region of the heart in more than 6 patients with heart disease with involvement of the coronary arteries. The results have been sufficiently encouraging to justify further exploration of this important problem.

Forty patients with angina pectoris have been treated neurosurgically by White [66] for the relief of pain which did not respond to medical treatment. Surgical excision of the upper thoracic ganglions has given

65. Beck, Claude S.: The Development of a New Blood Supply to the Heart by Operation, Ann. Surg. **102**:801, 1935. Beck, C. S., and Tichy, V. L.: The Production of a Collateral Circulation to the Heart: An Experimental Study, Am. Heart J. **10**:849, 1935. Moritz, A. R., and Beck, C. S.: The Production of a Collateral Circulation to the Heart: Pathological Anatomical Study, ibid. **10**: 874, 1935.

66. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935.

nearly perfect relief on the side on which operation was performed, but the procedure was found to be too dangerous. White has found the paravertebral injection of alcohol, on the other hand, to be a reasonably safe procedure. It gave excellent results in 67.7 per cent of the cases, and converted the severe forms of angina pectoris into milder types which could be more easily controlled by medical measures in another 17.6 per cent. In the remaining 14.7 per cent of cases pain was not satisfactorily relieved, but in each instance the signs of paralysis of the sympathetic nerves and complete anesthesia of the intercostal nerves was not produced. The technic and complications of paravertebral injection of alcohol are discussed.

There has been further evidence [67] of the beneficial effect of theophylline ethylene-di-amine in the treatment of heart disease with involvement of the coronary arteries. It was shown that this drug promotes the development of the collateral circulation in cases of experimentally induced cardiac infarction in the dog. Favorable clinical results are reported not only when theophylline is used in the treatment of acute coronary occlusion but also in instances of paroxysmal dyspnea and in cases of angina pectoris. The beneficial influence probably results from its action in promoting the extent of the collateral coronary circulation. The importance of long continued treatment is emphasized.

HEART FAILURE AND ITS TREATMENT

Harrison [68] has published a book of three hundred and forty-nine pages, entitled "Failure of the Circulation," which deals with studies carried out by himself and his colleagues on circulatory disorders as observed in patients with diseases of the heart and in experimental animals. The problem is approached from a clinicophysiologic aspect and, quite naturally, stresses the point of view of the author. In the final chapter his chief conclusions are summarized as follows:

> Aside from the coronary syndrome which is initially a local circulatory disturbance, general functional impairments of the cardiovascular system are of three main types, which may occur singly or in various combinations.
>
> I. Acute circulatory failure (the hypokinetic syndrome) includes the conditions which have usually been classified as "collapse," "primary shock" and "secondary shock." It may be of cardiac origin but is usually due to disturbances in the periphery. Its chief subjective manifestation is weakness and the most important

67. Fowler, W. M.; Hurevitz, H. M., and Smith, Fred M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, Arch. Int. Med. **56**:1242 (Dec.) 1935. Smith, Fred M.; Rathe, Herbert W., and Paul, W. D.: Theophylline in the Treatment of Disease of the Coronary Arteries, ibid. **56**:1250 (Dec.) 1935.

68. Harrison, Tinsley Randolph: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935.

objective signs are feeble pulse, tachycardia, decrease in the arterial blood pressure, and decline in the pulse pressure. Less constantly the heart sounds are diminished in intensity and approach each other in quality. These phenomena are dependent on or related to diminution of the cardiac output, which may be brought about in several different ways.

1. The hematogenic type of the hypokinetic syndrome, which has been called "secondary shock," is due to decrease in the circulating blood volume, such as occurs in hemorrhage, traumatic shock or following excessive dehydration from any cause.

2. The neurogenic type of the hypokinetic syndrome ("primary shock") is due to vascular dilatation dependent on disturbances in the nervous system, such as fainting, spinal anesthesia and injuries to the brain or spinal cord.

3. The vasogenic type of the hypokinetic syndrome is also brought about by dilatation of the arterioles, but is dependent on influences which act directly on the vessels, such as histamine and nitrites.

4. The cardiogenic type of the hypokinetic syndrome is usually produced by sudden severe damage to the heart, such as occurs in coronary thrombosis, or by prolonged beating as in persistent paroxysmal tachycardia. Less commonly this symptom-complex may be brought about by sudden and marked slowing of the heart, or by inadequate cardiac filling as the result of pericardial thickening. In such instances the manifestations of congestive heart failure and those of acute circulatory collapse may coexist.

II. The overactive heart (the hyperkinetic syndrome), like the hypokinetic disturbances, is usually of peripheral rather than of cardiac origin. Its chief subjective manifestation is palpitation and its objective phenomena are forcible diffuse cardiac impulse, loud heart sounds, apical and especially basal systolic murmurs, moderate tachycardia, increased arterial pulsations, bounding or even collapsing pulse, and increased pulse pressure. Its most common causes are hyperthyroidism, severe anemia, fever, and certain types of cardiac neurosis. Some of the last patients exhibit these phenomena only on mild exertion and to these the terms "neurocirculatory asthenia" (which is a misnomer), "soldier's heart" and "effort syndrome" have been applied. The phenomena of the hyperkinetic disturbance are similar to those which occur in normal persons during physical exertion and are due mainly to the same underlying physiological mechanism—increase in the cardiac output.

III. Congestive heart failure (the dyskinetic syndrome) designates the clinical picture usually called "cardiac decompensation." The primary disease process may involve either the heart—as in valvular diseases, or the peripheral vascular apparatus—as in hypertension, but in each instance the final result is to render the heart inefficient in the performance of its work. The main subjective manifestation of this syndrome is dyspnea, and the most important objective phenomena are cardiac enlargement, decrease in vital capacity, râles at the lung bases, distension of the systemic veins, enlargement of the liver, edema, and the accumulation of fluid in the body cavities.

This clinical picture has been believed by many to be dependent on inadequate blood supply to the tissues and it is true that accurate measurements of the cardiac output reveal low values in the majority of patients with congestive heart failure. However the thesis that dyspnea, edema, and the other important manifestations of congestive failure are dependent on diminished flow through the tissues is untenable for several reasons, of which the following are the most important.

(*a*) Edema and dyspnea are not usually present in patients with disorders, such as hemorrhage or traumatic shock, which are known to be associated with marked decrease in the cardiac output, and are not produced in experimental animals by diminution of the cardiac output.

(*b*) Some patients with congestive heart failure have values for the cardiac output which are well within the normal range. Disappearance of congestive heart failure is not associated with constant increase in the cardiac output even in patients who exhibit diminution of this function.

(*c*) Those therapeutic measures, such as venesection, and the use of digitalis and of diuretic drugs, which cause clinical improvement in persons with congestive heart failure, do not regularly cause an increase in the output of the heart.

This evidence seems to indicate conclusively that the "forward failure" (diminished output) theory is erroneous. On the other hand the alternate theory of "backward failure" ("back pressure") appears to fit the facts.

According to this hypothesis the essential factor in the production of the clinical manifestations of heart failure is accumulation of blood in those vascular areas which drain toward the failing chamber of the heart. Thus failure, i. e., dilatation, of the left ventricle leads to a rise in the pressure in the left auricle which causes engorgement of the lungs. Such an increase in the intrathoracic blood volume has been demonstrated not only by the findings at necropsy but also by measurements —made by indirect methods—during life. Since the amount of blood flowing through the lungs, i. e., the cardiac output, is not augmented the increase in the size of the pulmonary vascular bed must be associated with a diminution in the velocity of the blood flow, and this likewise has been demonstrated. Similar changes occur in the systemic circuit when the right ventricle fails. In most patients the underlying cause of cardiac disease is of such a nature as to impose the primary strain on the left side of the heart. If the "back pressure" theory is correct congestive phenomena should develop first in the lungs and later in the systemic circulation. This is exactly what occurs, as is shown by the fact that diminution in the vital capacity precedes an increase in the systemic venous pressure in almost all cases.

According to this (the "back pressure") theory the manifestations of cardiac failure are to be ascribed chiefly to a rise in pressure in the veins draining into the failing side of the heart. That cardiac edema is due to such a rise in systemic venous pressure is probably generally admitted. Concerning dyspnea no such agreement exists, many persons still ascribing it to diminished cerebral blood flow—an hypothesis which is, in the main, erroneous.

Investigations of cardiac dyspnea have shown that it occurs under conditions which cause labored breathing. The excessive respiratory effort and the subjective distress are not cause and effect but are parallel responses. Dyspnea, the subjective phenomenon, represents the effect on the cerebral cortex of the same factors which, when acting on the medulla, produce the labored breathing. The important point is that one can measure the respiratory effort and thereby can achieve a quantitative expression of its subjective concomitant, dyspnea. When there is no obstruction to respiration the breathing is labored in proportion to the closeness with which the actual ventilation approaches the maximum possible ventilation. The actual ventilation can be readily determined and the maximum possible ventilation depends on the vital capacity, which can also be easily measured. Simultaneous observation of these two functions allows a quantitative formulation of the degree of dyspnea.

The respiratory reserve can be encroached on and the breathing made to become labored by any process which either decreases the vital capacity or which increases

the ventilation. In patients with congestive heart failure the vital capacity is decreased as a result of congestion of the lungs. This predisposes the subject to dyspnea, but dyspnea may be absent as long as the breathing is not stimulated. The several types of cardiac dyspnea are to be attributed to various agents which cause respiratory stimulation in a patient with diminished respiratory reserve (decreased vital capacity). The study of the mechanism of cardiac dyspnea therefore resolves itself into an investigation of these agents.

It was formerly believed that dyspnea in cardiac disease could be attributed to chemical changes in the arterial blood as a result of inadequate pulmonary ventilation. Such alterations are encountered in moribund patients and in those who have severe pulmonary edema or advanced emphysema but are absent in the majority of patients with congestive failure. The concept that cardiac dyspnea is dependent on inadequate supply of blood to the respiratory center as a result of subnormal cardiac output has been shown to be erroneous by the observation that the composition of the blood in the internal jugular vein is not usually altered by procedures, such as mild exercise and the assumption of the recumbent posture, which cause dyspnea.

In general, the stimulation of breathing in persons with cardiac disease is of reflex rather than of chemical origin. Of the several reflexes concerned the most important one arises in the lungs, and is due to the effect of congestion on the afferent vagal endings. This reflex is mainly responsible for orthopnea and for cardiac asthma, and it is a factor in the production of dyspnea on exertion. Dyspnea on exertion, however, is more closely related to reflex respiratory stimulation from the moving muscles and from the action of an increased venous pressure, brought about by exertion, on the afferent vagal terminals in the venous end of the heart.

Dyspnea is then, in the main, to be ascribed to pulmonary congestion as a result of "back pressure" from the left side of the heart. The increase in pulmonary pressure eventually leads to failure of the right ventricle and edema. Dyspnea usually precedes edema because the underlying disease process ordinarily imposes the initial strain on the left side of the heart.

Unlike dyspnea and edema, enlargement of the heart, which is the other cardinal manifestation of cardiac disease, is not a result of heart failure, but is brought about by the same underlying disorder which produces heart failure.

Cardiac enlargement consists of two processes. One of them is hypertrophy which is dependent on overwork, either of the heart as a whole or of portions of it, as a result of disease of other parts. The thickening of the muscle fiber tends at first to make it more powerful. After a time this mechanical advantage is more than offset by a chemical disadvantage, for the recovery process in the heart muscle, being dependent on the diffusion of oxygen into it, becomes hampered by the thicker fiber. This is especially important when the heart rate is rapid, for in this condition the duration of diastole (the period in which recovery must take place) is diminished. Hence, even if the burden on the heart is not increasing, the hypertrophied heart tends to become fatigued. Fatigue leads to dilatation, which has the double advantage of diminishing the thickness and of increasing the surface of the fibers. Dilatation is the immediate response of the heart to increase in work and hence probably precedes hypertrophy as well as succeeding it. But dilatation—this second type of cardiac enlargement—has its disadvantages also. The dilated heart, in order to perform a given amount of work, requires more oxygen than does the undilated heart. If, because of the thickened fiber, coronary disease, or other factors, the needed oxygen is not available the heart will dilate still more and will require still more oxygen to perform its previous work. And so the cycle proceeds.

For these reasons the enlarged heart tends to become fatigued. Cardiac fatigue is a phenomenon of fundamental importance in relation to cardiac failure. When studied under conditions—such as exist in the heart-lung preparation—in which the various circulatory factors can be controlled and the action of the heart readily observed, it is found to take place in three stages which merge into each other gradually.

(*a*) The heart dilates, all other factors including the output remaining constant. This stage probably corresponds to the clinical condition of a patient who has no congestive phenomena but who has a limitation of effort, for the reserve power of a heart consists of its ability to dilate, and a heart which is already dilated has begun to encroach on its reserve.

(*b*) The output begins to diminish somewhat but returns to its previous level if the venous pressure is sufficiently raised. At the same time the degree of dilatation increases somewhat. This stage appears to correspond to the clinical state of a patient with a normal or nearly normal cardiac output but with a considerably dilated heart, and with increased venous pressure and consequent phenomena of congestive failure.

(*c*) The output diminishes rapidly and in a short time the heart ceases to beat. This is a terminal state and corresponds to the moribund patient with hypokinetic as well as dyskinetic phenomena.

The analogy with the experimentally fatigued heart allows us to define heart failure. It may be said to begin when, in order to perform a given amount of work, the diastolic volume of the heart increases. Expressed otherwise, it may be said that the reserve power of the heart is beginning to fail when the size of that heart is increased in proportion to its output. Similarly, congestive heart failure may be defined as a state in which venous pressure is increased disproportionately to the cardiac output, or as the condition in which the heart can maintain a given output only when driven to do so by a greater filling pressure.

My conclusion, then, is that the clinical manifestations of congestive heart failure are due to "back pressure," dyspnea being brought about by congestion of the lungs which is a result of "back pressure" from the left side of the heart, and edema being due to congestion of the systemic circulation dependent on "back pressure" from the right side of the heart. In both instances the rise in pressure in the veins is dependent on dilatation of the chambers of the corresponding side of the heart, the dilatation in its turn being a manifestation of fatigue of the cardiac muscle. The dilated heart is an inefficient pump for, although it may supply an adequate amount of blood to the tissues, it expends excess energy in order to carry on this work. Heart failure is to be attributed, in the main, to inefficiency rather than to insufficiency of the myocardium.

Vaquez [69] expressed the belief that there is a marked revival of interest in the study of digitalis, due chiefly to the widespread dissatisfaction with present galenic preparations which have enjoyed great preference because the total drug base is more useful than any one of its components and because of the practical ease of administration. He remarked that the variability in therapeutic activity and the instability of galenic preparations which have apparently caused so much

69. Vaquez, H.: Préparations galéniques et glucosides de la digitale, Arch. d. mal. du cœur **28**:185, 1935.

dissatisfaction in many places have not especially troubled clinicians in America. He told how the Hygiene Section of the League of Nations took up the study of standardization of galenic preparations but after five years' study concluded that it was still too early to make a decision as to the choice of a method of extraction of the drug or a method of standardization and that consequently an international unit cannot be fixed. Ingenious researches are described which were performed with the intention of isolating all the glucosides of digitalis, studying their several qualities and synthetically regrouping them so as to reconstruct the global activity of the drug. Up to the present these attempts have not met with great success.

Fraenkel [70] stated that it is possible to insure the same degree of accuracy in administering digitalis to patients as is demanded in a pharmacologic experiment on the lower animals, but in order to do this it is necessary to dispense with the galenic preparations and their many substitutes and, in addition, to change the usual routine of administration. When one considers the large variation in different galenic preparations, the decreased effect resulting from their reactions with the acid gastric juice and intestinal alkalis when they are given by mouth, the faulty absorption due to the surface activity and adsorption of the drug, and the incalculable loss under the pathologic conditions of circulatory failure, it must be concluded that the only suitable method of quantitative administration is intravenous injection.

In his choice of a drug Fraenkel was guided by the results of experiments on cats in which different glucosides of digitalis were compared as to the degree and duration of their action. Strophanthin Kombé was chosen because its action could be maintained by repeated injections without the appearance of toxic effects attributable to cumulative action of the drug. Tens of thousands of injections of this drug have been given to patients without there resulting any of the dreaded complications.

He cited a series of cases in which strophanthin was used only after the oral administration of digitalis had proved unsuccessful. Excellent therapeutic results were usually obtained. It was necessary to adhere to exact dosage and to note the effect of each dose. Patients who needed little strophanthin and displayed marked diuresis had, usually, a better prognosis than those who required larger doses yet lost edema fluid more slowly. Fraenkel stated:

> . . . it is by no means exclusively cases of heart failure with auricular fibrillation or frequent and regular pulse which respond to strophanthin administration.

70. Fraenkel, A.: Pharmacological Aspect of Digitalis Therapy, Lancet **2**: 1101, 1935.

Complete success is met with even when the pulse is infrequent and regular. In these cases the muscular effect of strophanthin is more prominent than the vagal. . . . This attempt, however, to evaluate a rational digitalis therapy from a knowledge of experimental pharmacology, and to describe the peculiar importance of the intravenous route in connection with the glucoside which is most suitable for this mode of administration, is not to be regarded as a revolt from the customary empirical use of preparations of digitalis by mouth. . . . Withering's therapy retains its position in the treatment of heart failure when such is not of too severe a degree or of not too long a standing.

Bedford and Campbell [71] have carried out clinical tests with strophanthin emini, which yields on analysis a complex mixture of glucosides similar in type to that obtained from strophanthin kombé. Strophanthin emini is best given intravenously and provokes a digitalis-like action on the heart in from fifteen to thirty minutes. It appears to act more quickly than digoxin,[72] which has recently been isolated and tested clinically. It has no advantage over digitalis and has one great disadvantage, in that the therapeutic and the toxic dose are so close together.

The recently isolated cardiac glucoside thevetin [73] has been subjected to further clinical trial. In clinical use it is best given intravenously. It has a digitalis-like action, with a potency about one-seventh that of ouabain. It appears to be more toxic than digitalis when comparable doses are given.

Carr and Mayer [74] have studied the effect of scillonin, a derivative of squill, on 104 patients with cardiac decompensation. This drug has the same therapeutic and toxic effects as digitalis. Because nausea appears as a late rather than as an early toxic effect of scillonin, that drug is of advantage for certain patients who take digitalis with difficulty because of gastric distress early in the course of medication. More care is required in the administration of scillonin, however, than in the use of digitalis.

Good clinical results have followed the use of diuretic drugs, either continuously or in long courses, in the early stages of heart failure. It is unfortunate that these drugs are not more commonly used before the advent of frank cardiac edema. This view has been reemphasized

71. Bedford, D. E.; Campbell, M., and Wood, P. H.: The Treatment of Auricular Fibrillation with Strophanthin Emini, Guy's Hosp. Rep. **85**:185, 1935.

72. Wayne, E. J.: Clinical Observations on Two Pure Glucosides of Digitalis, Digoxin, and Digitalinum Verum, Clin. Sc. **1**:63, 1933.

73. Arnold, Harry L.; Middleton, William S., and Chen, K. K.: The Action of Thevetin, a Cardiac Glucoside, and Its Clinical Application, Am. J. M. Sc. **189**:193, 1935.

74. Carr, James G., and Mayer, Jacob D.: Clinical Experience with a Derivative of Squill, Arch. Int. Med. **56**:700 (Oct.) 1935.

by Friedman and his co-workers,[75] who have frequently noticed the amelioration of cardiac symptoms after the administration of diuretics to patients with little or no demonstrable edema. Improvement occurred even when the diuresis was of slight degree. Objective measurements of the effect of diuretics on circulatory and respiratory functions were made on a group of hospitalized patients who complained chiefly of dyspnea but who had minimal pitting or latent edema. Clinical improvement was sometimes associated with an increase in vital capacity, but often this increase was so slight as to be of questionable significance. Decrease in spinal fluid pressure and in blood volume may have played a rôle, but these factors were not studied. Consistent changes in heart rate, oxygen consumption and cardiac output did not occur. Two possible factors probably influenced cardiac output following the administration of diuretic drugs. One was the decrease in flow of blood through the edematous tissues, which tended to decrease the cardiac output, and the other was the reduction of myocardial edema, which may have led to an increase in the cardiac output.

The changes in the alkali reserve and in the protein content of the blood following the use of diuretics have been investigated.[76] The results obtained by various workers are not in agreement regarding the mechanism whereby values for plasma protein rise after diuresis following the administration of salyrgan.

It is still too early to evaluate correctly the procedure of total thyroidectomy in the treatment of heart failure.[77] Three years' experi-

75. Friedman, Ben; Resnik, Harry; Calhoun, J. A., and Harrison, T. R.: Effect of Diuretics on the Cardiac Output of Patients with Congestive Heart Failure, Arch. Int. Med. **56**:341 (Aug.) 1935.

76. Bryan, A. Hughes; Evans, William A., Jr.; Fulton, Marshall N., and Stead, E. A., Jr.: Diuresis Following the Administration of Salyrgan: Its Effect on the Specific Gravity, the Total Nitrogen and the Colloid Osmotic Pressure of the Plasma of Normal and Edematous Dogs, Arch. Int. Med. **55**:735 (May) 1935. Schally, A. O.: Veränderungen der Bluteiweisskörper bei der Salyrgandiurese, Deutsches Arch. f. klin. Med. **177**:368, 1935. Gottsegen, G.: Einfluss der Diuretika auf die Alkalireserve des Blutes, Wien. klin. Wchnschr. **48**:1116, 1935.

77. Berlin, David D.: Total Thyroidectomy for Intractable Heart Disease: Summary of Two and One-Half Years' Surgical Experience, J. A. M. A. **105**: 1104 (Oct. 5) 1935. Blumgart, H. L.; Berlin, D. D.; Davis, D.; Riseman, J. E. F., and Weinstein, A. A.: Total Ablation of Thyroid in Angina Pectoris and Congestive Failure: XI. Summary of Results in Treating Seventy-Five Patients During the Last Eighteen Months, ibid. **104**:17 (Jan. 5) 1935. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Weinstein, A. A.: Treatment of Angina Pectoris and Congestive Failure by Total Ablation of the Normal Thyroid: XIV. Results in Arteriosclerotic Heart Disease, Am. Heart J. **10**:596, 1935. Clark, Richard J.; Means, James H., and Sprague, Howard B.: Total Thyroidectomy

(Footnote continued on next page)

ence indicates that this operation is of significant value when limited to a few carefully selected cases. Its greatest value, by far, is in the treatment of angina pectoris, but even in cases of that disorder there is no cause for great enthusiasm, and certain conditions must be fulfilled before thyroidectomy is suggested (not urged). The probable life expectancy of the patient without operation must be at least from one to two years. In patients with angina pectoris the presence of complicating disease of significant degree, especially of involvement of the heart, lungs, kidneys or liver, has to be ruled out. It must be shown that available medical treatment, including rest in bed for one month, is inadequate. Furthermore, the preoperative basal metabolic rate must not be lower than —15 per cent. Technically the operation does not involve undue risk when skilfully performed. If these criteria are given full consideration, one may with confidence predict genuine improvement in regard to anginal attacks in about three fourths of the cases.

Available studies indicate a wide divergence of opinion regarding the value of thyroidectomy in patients with congestive heart failure; a few patients are undoubtedly suitable for this procedure. It is impossible here to discuss adequately the difficult problem of selection of cases. Reference may be made to the aforementioned reports.

---

for Heart Disease: Experiences with Twenty-One Patients at the Massachusetts General Hospital, New England J. Med. **214**:277, 1935. Levine, S. A., and Eppinger, E. C.: Further Experiences with Total Thyroidectomy in the Treatment of Intractable Heart Disease, Am. Heart J. **10**:736, 1935. Riseman, J. E. F.; Gilligan, D. R., and Blumgart, H. L.: Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland: XVI. The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy, Arch. Int. Med. **56**:38 (July) 1935.

Book Reviews

Arthritis and Rheumatoid Conditions: Their Nature and Treatment. By Ralph Pemberton. Price, $5.50. Pp. 455, with 69 engravings and a colored plate. Philadelphia: Lea & Febiger, 1935.

The long-overdue second edition of this work, the first edition of which was published in 1929, will be warmly received. First written to help place the subject of arthritis on a plane which would arouse the interest and attention then lacking, the work now attempts to incorporate data which have accumulated in the past six years. Consequently the volume has been expanded one hundred pages, and many illustrations have been added.

The book maintains its same general order, starting with a brief historical approach, leading to arthritis as an economic problem and then to its pathology, dynamic pathology, symptomatology and treatment and to related conditions. One is impressed by the statistics quoted showing the magnitude of arthritis as a social problem. Surveys show that cases of this condition constitute 9 per cent of all cases of disease, outstripping those of tuberculosis and organic heart disease and outranked only by cases of accidents. In general, Pemberton follows the classification of Nichols and Richardson and that of Knaggs in classifying arthritis into atrophic and hypertrophic types. However, he believes that these types have many features in common and discusses the etiology and treatment with regard to the syndrome of the disease as a whole. Under "Dynamic Pathology" are discussed the influences of basal metabolism and of protein, lipoid, carbohydrate, salt and water metabolism, as well as the acid-base balance, circulatory, respiratory, cutaneous and renal function and the blood picture. Many of the discussions are unduly long in relationship to their importance, as is the space allotted to a review of the author's experiments which gave negative results. Changes in the circulation and in the carbohydrate metabolism are of especial interest.

Approximately 175 of the 455 pages are devoted specifically to treatment. All the important aspects are discussed—focal infection, the rôle of the intestine, diet, colonic irrigation, vaccines, physical therapy, drugs and medicinal measures. All are evaluated principally in the light of the author's own extensive experience. He seeks to recommend no one factor of therapy alone but to emphasize that the factors known to have a favorable influence should be coordinated into a whole, with necessary individualization.

The second edition insures this volume a continued important place in medical literature.

Thérapeutique de l'ulcère gastro-duodénal. By Jean Gatellier and François Moutier. Price, 22 francs. Pp. 236. Paris: Gaston Doin & Cie, 1935.

In this monograph Gatellier and Moutier present to the medical profession their experiences with the therapeutics for gastroduodenal ulcer. The material is derived from 1,200 personally treated patients. There is no bibliography or review of the literature on the subject. The authors merely report their experiences and occasionally refer to the work of physicians prominent in this field.

Practically the entire discussion is devoted to treatment. The first few pages contain a dissertation on the anatomic, clinical and pathologic aspects of the disease. Throughout the monograph brief discussions of the clinical manifestations of the various phases and complications of the condition, such as hemorrhage, perforation, obstruction and the like, that are being treated by one method or another, are given. They include a discussion of the findings in roentgenologic, gastroscopic and other special examinations, when these were used in the study of the cases.

The therapeutic presentation includes a consideration of the medical and surgical treatment of uncomplicated and complicated forms. The authors discuss preoperative and postoperative treatment, emphasizing joint medical and surgical treatment in these cases. They present a list of diets, prescriptions for patients and formulas for large quantity preparations of mixtures of drugs which they employed in the treating of their patients. The indications and rationale for their various therapeutic methods of choice under diverse conditions are also briefly presented.

From the monograph one realizes that the authors do not present any definitely superior method for the treatment of gastroduodenal ulcer and that they experienced results and difficulties with their methods similar to those obtained by different methods employed by other physicians. Nothing revolutionary is presented, but one who is interested in the therapy employed by the authors in treating their large series of patients can adequately learn it from this intelligible presentation.

Clinical Laboratory Methods and Diagnosis. By R. B. H. Gradwohl, M.D., director of the Gradwohl Laboratories, St. Louis. Price, $8.50. Pp. 1028, with 328 illustrations and 24 color plates. St. Louis: C. V. Mosby Company, 1935.

Gradwohl in his preface states that this book was written to help the clinician, the laboratory worker and the medical student to learn laboratory diagnosis. It is divided into seventeen chapters more or less according to the traditional fashion for a textbook of this nature. The division of the space allotted to different subjects is of some interest, as it reflects so well current medical enthusiasms; 64 pages are devoted to urinalysis, 81 to blood chemistry, 181 to hematology and 155 to clinical bacteriology. The standard picture of the accepted procedures in the different fields is given in great detail. A carefully written chapter is devoted to the subject of postmortem examinations, telling how to obtain permission to make such examinations, and, permission having been granted, how to perform them most perfectly.

On the whole, the volume is a happy venture. As is stated in the review which appeared in *The Journal of the American Medical Association* (**104**:2291 [April 22] 1935), the book is an unusually complete work on clinical laboratory methods and their interpretation and is a fertile source of information.

The Treatment of Diabetes Mellitus. By Elliott P. Joslin, M.D., with the cooperation of Howard F. Root, M.D.; Priscilla White, M.D., and Alexander Marble, M.D. Fifth edition. Price, $6. Pp. 620, with 144 tables and 7 illustrations. Philadelphia: Lea & Febiger, 1935.

In his preface to the new edition Joslin states: "Diabetes is a disease for young doctors," and acting in this spirit one finds that Root, White, Marble and others are now associated with him in writing certain sections. The senior author shows, however, no signs of age or decay and deals with the subject with all his former vigor and clarity. Since the previous (1928) edition the book has been shortened by about four hundred pages, but in spite of this the reviewer fails to discover any phase or, indeed, any detail of diabetes which is not adequately discussed. "Joslin" definitely remains the standard guide for American practice; a sound, well tempered point of view is maintained, going neither to one extreme nor the other on the matter of carbohydrate ration; each point is buttressed against the solid background of the author's vast clinical experience as well as statistics from the literature. The chapters on the complications of diabetes, diabetic surgery, diabetes in childhood and pregnancy in diabetes contain valuable material not readily accessible elsewhere in textbooks.

Human Pathology. By Howard T. Karsner, Professor of Pathology, Western Reserve University. With an introduction by Simon Flexner. Fourth edition, revised. Price, $10. Pp. 1013, with 18 colored and 443 plain illustrations. Philadelphia: J. B. Lippincott Company, 1935.

Karsner's "Human Pathology" has been accepted widely as a text by teachers, students and practitioners of medicine. The fourth edition, now offered, has been revised and extended to include some of the more recent advances in pathology. Certain chapters have been rewritten completely. The general plan of arrangement is essentially the same as in the preceding editions. The twelve chapters of the first part concern general pathology; the ten of the second part are special. The preceding editions have been used largely by undergraduate students of medicine and has been an excellent text for them. The fourth edition will serve the same general group and is recommended to instructors of general and special pathology in medical schools for the guidance of their students.

Diseases of the Liver, Gall Bladder, Ducts and Pancreas. By Samuel Weiss. Price, $10. Pp. 1099, with 358 illustrations and 6 plates. New York: Paul B. Hoeber, Inc., 1935.

This monumental compendium cannot be reviewed in detail in the space available. Gotten up in the beautiful Hoeber format, with a wealth of excellent illustrations and an extensive bibliography and index, it contains an encyclopedic account of practically everything pertaining to the liver, gallbladder and pancreas. To the reviewer the value of the book lies not so much in the discussions of common topics which are adequately dealt with in ordinary textbooks as in the collection of all sorts of rare disorders and anomalies information about which is usually obtainable only in the periodic literature. This encyclopedic form of treatment sometimes disturbs the perspective a little and makes it hard to separate what is of established value from material which is less useful, but this can hardly be avoided in a reference book of this sort. The price is reasonable. It is perhaps to be regretted that the work was not divided into two volumes, as the book is heavy and difficult to handle.

Abnormal Arterial Tension. By Edward J. Stieglitz, M.D., Assistant Clinical Professor of Medicine, Rush Medical College. Price, $3. Pp. 261, with 66 illustrations. New York: National Medical Book Company, Inc., 1935.

This book is one of a series of the National Medical Monographs edited by Dr. Morris Fishbein. The other subjects so far discussed in the series are obstetrics, industrial medicine, colitis and diseases of the skin and chest. One gathers that the National Medical Monographs are not unlike similar medical monographic systems that have appeared recently in France and are designed especially to be of use to physicians in this country.

This particular book by Dr. Stieglitz is nice-looking. It slips easily into one's pocket, so that it can be read at odd moments. It is well printed. It is simply written in clear, concise English. The illustrations and diagrams are excellent. The various aspects of normal arterial tension and what is known about the cause and treatment of hypertension and hypotension are intelligently discussed in the light of present knowledge. On the whole, the book should prove a useful member of its group.

Experimentel Pneumothorax. By Kjeld Tørning. Paper. Pp. 161, with 31 figures and 79 protocols. Copenhagen: Nyt Nordisk Forlag, 1933.

This dissertation reviews the history of therapeutic pneumothorax and the theories of its modus operandi and gives the results of Tørning's experiments on animals. Of the usual laboratory animals, the rabbit is the only one that has a sufficiently rigid mediastinum to be useful in the study of unilateral collapse. A

new technic was used to study the rates of ventilation of the two lungs separately without opening the pleural cavity or injuring the thoracic skeleton. The changes in the ventilation of the two sides are described in detail for open, and for various degrees of closed, unilateral pneumothorax. Measurements of the rate of oxygen consumption and the degree of oxygenation of the arterial blood were used to calculate the rate of circulation through the lungs and enabled Tørning to show that in a collapsed lung the circulation is so reduced that it may sink to less than 15 per cent of the total pulmonary circulation.

Living Along with Heart Disease. By Louis Levin, M.D., cardiologist to the St. Francis Hospital and New Jersey State Prison Hospital, Trenton, N. J. Price, $1.50. Pp. 126. New York: The Macmillan Company, 1935.

This is a manual for patients with heart disease, not unlike the manuals on diabetes or similar works already available for the inquisitive layman. It is intelligently written and discusses heart disease fairly and honestly, enlivened from time to time by apt anecdotes of cases in places that otherwise might seem gloomy or depressing. Levin states that the purpose of the book is to present to the reader a simplified explanation of various aspects of heart disease with the ultimate hope of instilling sane optimism in the patient's philosophy regarding this disorder. He has accomplished a step in the right direction.

News and Comment

AMERICAN HEART ASSOCIATION, INC.

The Twelfth Scientific Session of the American Heart Association will be held on Tuesday, May 12, 1936, from 9:30 to 5:30 p. m., at Hotel Phillips, Kansas City, Mo. The program will be devoted to cardiac insufficiency.

CORRECTION

In the article by Dr. M. M. Wintrobe in the February issue (ARCH. INT. MED. **57**:289, 1936), on page 293, line 10, "inversely proportional to the degree of anemia" should read "inversely proportional to the number of red cells."